

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

_____)	
WYETH,)	
)	
)	
Plaintiff,)	
)	Civil Action No.: 06-222 JJF
v.)	
)	
IMPAX LABORATORIES, INC.,)	PUBLIC VERSION
)	
Defendant.)	
_____)	

**EXHIBITS TO THE DECLARATION OF KAREN JACOBS LOUDEN
IN SUPPORT OF WYETH'S OPENING MARKMAN BRIEF**

VOLUME 2 OF 3

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WYETH 002-000790

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DEBORAH MARIE SHERMAN, PLATTSBURGH, NY.

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EXTENDED RELEASE FORMULATION

U.S. DEPT. OF COMM./PAT. & TM--PTO-436L (Rev.12-84)

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WYETH 002-000791

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Case Docket No. AHP-95011

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Transmitted herewith for filing is the patent application of

Inventor: SHERMAN

For: EXTENDED RELEASE FORMULATION

Enclosed are:

- ☐ _____ sheets of drawings
- ☐ A certified copy of a _____ application
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WYETH 002-000793

AHP-95011



EXTENDED RELEASE FORMULATION

This application claims priority to Provisional Application No. 60/014,016 filed March 25, 1996.

Background of the invention

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/antiinflammatory drug etodolac (Lodine®) appears in US patent 4,966,768. US patent 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, chopped into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. Gelatin capsules are filled with the film-coated spheroids in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a gelatin capsule to obtain desired release rates and blood levels. US patent 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propranolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in US patent 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

Brief Description of the Invention

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with

venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

5 The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over
10 conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

15
Detailed Description of the Invention

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the
20 kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

25 The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about
30 two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent
35 hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35

percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropyl methylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film
5 coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropyl methylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a
10 viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing
15 the inventive concept.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were
20 either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40–50% dissolution at 2 hrs, 60–70% dissolution at 4 hrs and 85–100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of
25 microcrystalline cellulose and hydroxypropyl methylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids.
30 Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride–microcrystalline cellulose mix made production of spheroids practical.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this
35 invention.

Example 1.

VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES

A mixture of 44.8 parts (88.4 % free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropyl methylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into hard gelatin capsules conventionally.

Example 2.

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

Example 3.

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

Example 4.

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C. Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids

or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

5

Table 1

Acceptable Coated Spheroid Dissolution Rates

<u>Time (hours)</u>	<u>Average % Venlafaxine HCL released</u>
2	<30
4	30-55
8	55-80
12	65-90
24	>80

10

15

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into hard gelatin capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

20

25

30

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution. The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

35

where A_s is absorbance of sample preparation, W_r is weight of reference standard, mg; S is strength of the reference standard, decimal; V_1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, A_r is the absorbance of the standard preparation, V_2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

Table 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 x 75 mg (ER)capsules (q 24 hr)	1 x 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

5

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

10

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat

below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

- 5 Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the
10 plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

15 **Table 3. Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level**

Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

5 The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20°C until analysis could be completed.

10 To 1 mL of each plasma sample in a plastic tube was added 150 µL of a stock internal standard solution (150 µg/mL). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 µL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each 15 tube, vortexed, and 50 µL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm x 4.6 mm, 5 µ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

20 Thus, the desired dissolution rate of a sustained release dosage form of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a hard gelatin capsule containing a therapeutically effective amount of spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and hydroxypropyl methylcellulose coated with ethyl cellulose and hydroxypropylmethylcellulose.
2. An extended release formulation according to claim 1 wherein the spheroids are composed of about 37.3% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62.17% by weight of microcrystalline cellulose.
3. A composition according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).
4. A composition according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.04% of total weight) and hydroxypropylmethylcellulose (0.714% of total weight).
5. A composition according to claim 1 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).
6. A film coating composition which is composed of ethyl cellulose (15% of total weight), having a 44.0-51.0% content of ethoxy groups, and hydroxypropylmethylcellulose (85% of total weight) having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.
7. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 15% ethyl cellulose type HG 2834 and 85% hydroxypropyl-methylcellulose type 2910 sufficient to give coated spheroids having a dissolution profile which gives the desired release rate over a 24 hour period.

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- ⁷
8. An extended release formulation of venlafaxine hydrochloride according to claim ⁶ ~~7~~ which provides lower peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.
- ⁸
5 9. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, ^{the} an encapsulated, extended release formulation ^{of claim 1 which} provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.
- ⁹
10. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of which comprises administering orally to a patient in need thereof, ^{the} an encapsulated, extended release formulation ^{of claim 1 which} provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

ABSTRACT

EXTENDED RELEASE FORMULATION

5 This invention relates to a 24 hour extended release dosage formulation and unit
dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better
control of blood plasma levels than conventional tablet formulations which must be
administered two or more times a day and further provides a lower incidence of nausea and
vomiting than the conventional tablets.

10

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **EXTENDED RELEASE FORMULATION**, the specification of which is attached hereto unless the following box is checked:

☐ was filed on _____ as United States Application Number or PCT Application Number _____ and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	Priority Claimed <input type="checkbox"/> Yes <input type="checkbox"/> No
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I hereby claim the benefit under Title 35 United States Code, §119(e) of any United States Provisional application(s) listed below.

60/014,006 (Application Number)	3/25/96 (Filing Date)
_____ (Application Number)	_____ (Filing Date)

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

(8) Egon E. Berg, Reg. No. 21,117; Ronald W. Alice, Reg. No. 27,609; both of Five Giralda Farms, Madison, New Jersey 07940-0874; and Arthur G. Seifert, Reg. No. 28,040; George Tarnowski, Reg. No. 27,472; Robert Wiser, Reg. No. 24,457; Arnold S. Milowsky, Reg. No. 35,288; Steven R. Eck, Reg. No. 36,126; all of P.O. Box 8299, Philadelphia, Pennsylvania, 19101; and Robert F. Boswell, Jr., Reg. No. 35,072 of 1407 Cummings Drive, Richmond, Virginia 23220.

Address all telephone calls to Robert F. Boswell, Jr., at telephone number (804)257-3613.

Address all correspondence to Ronald W. Alice, American Home Products Corporation, Patent Law Department, One Campus Drive, Parsippany, NJ 07054.

100 Full name of sole or first inventor Deborah Marie Sherman

Inventor's signature

Deborah Marie Sherman

18 Mar 97

Date

Residence 5 Belmont Avenue, Plattsburgh, New York 12901

Citizenship United States of America

Post Office Address Same as residence

Full name of second joint inventor _____

Inventor's signature _____

Date

Residence _____

Citizenship _____

Post Office Address _____



WYETH 002-000809

JUL 30 '97 11:23AM W R COI TANCE

P.1/5

AMERICAN HOME PRODUCTS

LAW DEPARTMENT

Patent Section

Richmond Office
A. H. Robins Co.
1407 Cummings Drive
Richmond, Virginia 23220

FACSIMILE TRANSMISSION

Attention:	Examiner Amy Hulina
Company:	USPTO
Fax Number	703-305-5408
T:	703-308-2974
From:	R. F. Boswell, Jr.
T:	(804) 257-3613
Fax Number	(804) 257-2168
Date:	July 30, 1997
Pages (including this page):	5

Message: Enclosed is a copy of the IDS submitted on July 10, 1997.

CONFIDENTIALITY NOTE

IMPORTANT: This message and any documents accompanying it are intended for the use of the individual or entity to which they are transmitted and may contain information that is privileged, confidential and exempt from disclosure under applicable laws. If the reader of this communication is not the intended recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by telephone and return the original communication to us at the address above via the U.S. Postal Service. We will reimburse you for the mailing costs. **THANK YOU.**

WYETH 002-000810

JUL 30 '97 11:23AM W R COM ANCE

P. 2/5

Docket No. AHP-95011

RECEIVED BY THE UNITED STATES PATENT OFFICE ON DATE
STAMPED BELOW

Paper Information Disclosure Statement

Applicant Sherman

Application No. 08/821,137

Filing Date 3/20/97

Group No.

Examiner

Express Mail

Mailed 7/10/97

WYETH 002-000811

JUL 30 '97 11:24AM W R CON ANCE

P.3/5

AHP-95011
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: SHERMAN

Application No.: 08/821,137

Group Art Unit:

Filed: 3/20/97

Examiner:

For: EXTENDED RELEASE FORMULATION

Assistant Commissioner for Patents
Washington, DC 20231

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT WITHIN
THREE MONTHS OF FILING OR BEFORE MAILING OF FIRST OFFICE
ACTION

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231, on the date appearing below.

Robert F. Boswell, Jr.

Robert F. Boswell, Jr.
(Typed or printed name of person mailing paper)

DATE

July 10, 1997

Respectfully submitted,

Robert F. Boswell, Jr.

Robert F. Boswell, Jr.
Registration No. 35,072

Dated:

July 10, 1997
Telephone: (804)257-3613

WYETH 002-000812

JUL 30 '97 11:24AM W R COM INCE

P.4/5

#11/2 G.P.
08-06-97

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : **Sherman**

Application No.: 08/821,137 Group Art Unit:

Filed: 3/20/97 Examiner:

For: **EXTENDED RELEASE FORMULATION**

INFORMATION DISCLOSURE STATEMENT UNDER RULE 97

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Applicants submit herewith patents, publications or other information of which they are aware, which they believe to be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 CFR 1.56. The filing of this information disclosure statement shall not be construed as a representation that a search has been made (37 CFR 1.56(g)), an admission that the information cited is, or is considered to be, material to patentability or that no other material information exists.

The filing of this information disclosure statement shall not be construed as an admission against interest in any manner. Notice of January 9, 1992, 1135 O.G. 13-25, at 25.

The references submitted are listed on the accompanying Form PTO-1449.

Copies of the listed patents, publications or abstracts thereof are enclosed herewith.

Respectfully submitted,

Robert F. Boswell, Jr.

Robert F. Boswell, Jr.
Registration No. 35,072

Dated: July 10, 1997
Telephone: (804)257-3613

WYETH 002-000813

WYETH 002-000814



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/821,137	03/20/97	SHERMAN	D AHP-95011

15M2/0805
RONALD W. ALICE
AMERICAN HOME PRODUCTS CORPORATION
ONE CAMPUS DRIVE
PARSIPPANY NJ 07054

EXAMINER

HULINA, A

ART UNIT	PAPER NUMBER
----------	--------------

1501

DATE MAILED:

08/05/97

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

- (1) Amy Hulina (3) _____
(2) Robert Boswell, Jr. (4) _____

Date of interview: 7/30/97Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative)...Exhibit shown or demonstration conducted: ☐ Yes ☒ No If yes, brief description: _____Agreement ☒ was reached. ☐ was not reached.Claim(s) discussed: 6, 9 and 10Identification of prior art discussed: Upton et al. (5,506,270)

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Agreed to amend claims 9 and 10 to depend from claim 1 to avoid rejection over Upton which discloses extended release venlafaxine at col 3 lines 25-27

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

Manual of Patent Examining Procedure, Section 713.04 Substance of Interview must Be Made of Record

A complete written statement as to the substance of any face-to-face or telephone interview with regard to an application must be made of record in the application, whether or not an agreement with the examiner was reached at the interview.

§1.133 Interviews

(b) In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for response to Office action as specified in §§ 1.111, 1.135. (35 U.S.C.132)

§ 1.2. Business to be transacted in writing. All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete a two-sheet carbon interleaf Interview Summary Form for each interview held after January 1, 1978 where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks in neat handwritten form using a ball point pen. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below.

The Interview Summary Form shall be given an appropriate paper number, placed in the right hand portion of the file, and listed on the "Contents" list on the file wrapper. The docket and serial register cards need not be updated to reflect interviews. In a personal interview, the duplicate copy of the Form is removed and given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephonic interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the telephonic interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Serial Number of the application
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (personal or telephonic)
- Name of participant(s) (applicant, attorney or agent, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the claims discussed
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). (Agreements as to allowability are tentative and do not restrict further action by the examiner to the contrary.)
- The signature of the examiner who conducted the interview
- Names of other Patent and Trademark Office personnel present.

The Form also contains a statement reminding the applicant of his responsibility to record the substance of the interview.

It is desirable that the examiner orally remind the applicant of his obligation to record the substance of the interview in each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check a box at the bottom of the Form informing the applicant that he need not supplement the Form by submitting a separate record of the substance of the interview.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner, to include, all of the applicable items required below concerning the substance of the interview:

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,
- 2) an identification of the claims discussed,
- 3) an identification of specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner. The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he feels were or might be persuasive to the examiner,
- 6) a general indication of any other pertinent matters discussed, and
- 7) If appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete or accurate, the examiner will give the applicant one month from the date of the notifying letter or the remainder of any period for response, whichever is longer, to complete the response and thereby avoid abandonment of the application (37 CFR 1.135(c)).

Examiner to Check for Accuracy

Applicant's summary of what took place at the interview should be carefully checked to determine the accuracy of any argument or statement attributed to the examiner during the interview. If there is an inaccuracy and it bears directly on the question of patentability, it should be pointed out in the next Office letter. If the claims are allowable for other reasons of record, the examiner should send a letter setting forth his or her version of the statement attributed to him. If the record is complete and accurate, the examiner should place the indication "Interview record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

WYETH 002-000851



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
---------------	-------------	-----------------------	---------------------

08/821,137 03/20/97 SHERMAN

D AHP-95011

15M2/0805

RONALD W. ALICE
AMERICAN HOME PRODUCTS CORPORATION
ONE CAMPUS DRIVE
PARSIPPANY NJ 07054

HULINA, A

ART UNIT PAPER NUMBER

1501

DATE MAILED

08/05/97 8:45

NOTICE OF ALLOWABILITY

PART I

1. ☒ This communication is responsive to 7/30/97
2. ☒ All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. ☒ The allowed claims are 1-5, 7-10
4. ☐ The drawings filed on _____ are acceptable.
5. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received, ☐ not been received, ☐ been filed in parent application Serial No. _____ filed on _____
6. ☒ Note the attached Examiner's Amendment.
7. ☒ Note the attached Examiner Interview Summary Record, PTOL-413.
8. ☒ Note the attached Examiner's Statement of Reasons for Allowance.
9. ☒ Note the attached NOTICE OF REFERENCES-CITED, PTO-892.
10. ☒ Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. ☐ APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
 - a. ☐ Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
 - b. ☐ The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
 - c. ☐ Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
 - d. ☐ Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:

- ☒ Examiner's Amendment
- ☒ Examiner Interview Summary Record, PTOL-413
- ☒ Reasons for Allowance
- ☒ Notice of References Cited, PTO-892
- ☒ Information Disclosure Citation, PTO-1449

- ☐ Notice of Informal Application, PTO-152
- ☐ Notice re Patent Drawings, PTO-948
- ☐ Listing of Bonded Draftsmen
- ☐ Other

Amy Hulina
Amy Hulina
Primary Examiner
Group 1500

WYETH 002-000852

Serial Number: 08/821,137

Page 2

Art Unit:

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:
 - I. Claims 1-5,7-10, drawn to a composition and method, classified in class 424, subclass 461.
 - II. Claim 6, drawn to a film coating, classified in class 427, subclass 3.
2. The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because claim 1 does not require the specific ethyl cellulose and hydroxypropylmethylcellulose in the particular amounts recited in claim 6. The subcombination has separate utility such as a film coating.
3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.
4. During a telephone conversation with Robert Boswell, Jr. on 7/30/97 a provisional election was made with traverse to prosecute the invention of I, claims 1-5,7-10. Affirmation of this election must be made by applicant in responding to this Office action. Claim 6 is withdrawn

WYETH 002-000853

Serial Number: 08/821,137

Page 3

Art Unit:

from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Robert Boswell, Jr. on 7/30/97.

6. The application has been amended as follows:

7. Claim 6 has been cancelled.

8. In claim 9, line 3, after "thereof", "an" has been changed to "the"; in line 4, after "formulation", ---of claim 1--- has been inserted; in line 4, after "formulation", "that" has been changed to "which".

9. In claim 10, line 3, after "thereof", "an" has been changed to "the"; in line 4, after "formulation", ---of claim 1--- has been inserted; in line 4, after "formulation", "that" has been changed to "which". The following is an examiner's statement of reasons for allowance: The prior art does not teach or suggest the specific extended release claim formulation according to claim 1.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue

WYETH 002-000854

Serial Number: 08/821,137

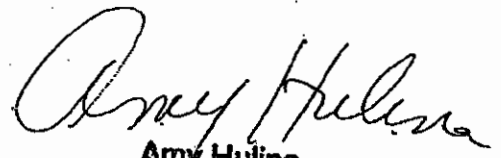
Page 4

Art Unit:

fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy Hulina whose telephone number is (703) 308-2974.


Amy Hulina
Primary Examiner
Group 1500

AH

August 4, 1997

WYETH 002-000855

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 2-82)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		SERIAL NO. 08/821,137	GROUP/ART UNIT 1501	ATTACHMENT TO PAPER NUMBER 3	
NOTICE OF REFERENCES CITED				APPLICANT(S) Sherman			
U.S. PATENT DOCUMENTS							
	DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE	
A	5506270	7/96	Upton et al	514	730		
B	5532244	7/96	Wong et al	514	255		
C	5530013	6/96	Husbands et al	514	330		
D	4535186	8/85	Husbands et al	564	336		
E	4761501	8/88	Husbands et al	564	167		
F							
G							
H							
I							
J							
K							
FOREIGN PATENT DOCUMENTS							
	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. PP. DWG. SPEC.
L							
M							
N							
O							
P							
Q							
OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)							
R							
S							
T							
U							
EXAMINER C. Hulse		DATE 7/30/97					

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

WYETH 002-000856

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

PATENT NO. : 4,535,186
DATED : August 13, 1985
INVENTOR(S) : G. E. Morris Husbands et al.
PATENT OWNER : American Home Products

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

FIVE YEARS

from the original expiration date of the patent, December 13, 2002, subject to the requirements of 35 U.S.C. § 41, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).



I have caused the seal of the Patent and Trademark
Office to be affixed this 25th day of April 1996.

Bruce A. Lehman

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

WYETH 002-000892


UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: Box ISSUE FEE
 ASSISTANT COMMISSIONER FOR PATENTS
 WASHINGTON, D.C. 20231

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

15M2/0805

RONALD W. ALICE
 AMERICAN HOME PRODUCTS CORPORATION
 ONE CAMPUS DRIVE
 PARSIPPANY NJ 07054

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/821,137	03/20/97	009	HULINA, A	1501 08/05/97
First Named Applicant	SHERMAN, DEBORAH MARIE			

TITLE OF INVENTION
 EXTENDED RELEASE FORMULATION

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 AHP-95011	424-456.000	009	UTILITY	NO	\$1290.00	11/05/97

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.
 If the SMALL ENTITY is shown as yes, verify your current SMALL ENTITY status:

- A. If the status is changed, pay twice the amount of the FEE DUE shown and notify the Patent and Trademark Office of the change in status, or
- B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

- A. Pay FEE DUE shown above, or
- B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "6b" of Part B should be completed.

II. All communications regarding this application must give application number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Patents Issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

3. PATENT AND TRADEMARK OFFICE COPY

AHP-95011

#4

8-22-97



Application No.: 08/821,137

Filed: 3/20/97

: Sherman

Group Art Unit:

Examiner:

JUL 30 1997
RECEIVED

For: EXTENDED RELEASE FORMULATION

INFORMATION DISCLOSURE STATEMENT UNDER RULE 97

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Applicants submit herewith patents, publications or other information of which they are aware, which they believe to be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 CFR 1.56. The filing of this information disclosure statement shall not be construed as a representation that a search has been made (37 CFR 1.56(g)), an admission that the information cited is, or is considered to be, material to patentability or that no other material information exists.

The filing of this information disclosure statement shall not be construed as an admission against interest in any manner. Notice of January 9, 1992, 1135 O.G. 13-25, at 25.

The references submitted are listed on the accompanying Form PTO-1449.

Copies of the listed patents, publications or abstracts thereof are enclosed herewith.

Respectfully submitted,

Robert F. Boswell, Jr.
Registration No. 35,072

Dated: July 10, 1997
Telephone: (804)257-3613

WYETH 002-000908

AHP-95011
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: SHERMAN

Application No.: 08/821,137

Group Art Unit:

Filed: 3/20/97

Examiner:

For: EXTENDED RELEASE FORMULATION

Assistant Commissioner for Patents
Washington, DC 20231TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT WITHIN
THREE MONTHS OF FILING OR BEFORE MAILING OF FIRST OFFICE
ACTION

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231, on the date appearing below.

Robert F. Boswell, Jr.

(Typed or printed name of person mailing paper)

DATE

Respectfully submitted,

Robert F. Boswell, Jr.
Registration No. 35,072

Dated:

Telephone: (804)257-3613

WYETH 002-000909

U.S. PATENT DOCUMENTS

FOREIGN PATENT DOCUMENTS

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

DATE CONSIDERED

WYETH 002-000910


**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/821,137	03/20/97	SHERMAN	D AHP-95011

 75F1/0203
 RONALD W. ALICE
 AMERICAN HOME PRODUCTS CORPORATION
 ONE CAMPUS DRIVE
 PARSIPPANY NJ 07054

EXAMINER	
HULINA, A	
ART UNIT	PAPER NUMBER
1501	05

DATE MAILED:

02/03/98

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☐ Applicant's failure to respond to the Office letter, mailed _____.
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☒ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of 08/05/97 of the Notice of Allowance.

☐ The issue fee was received on _____

☐ The issue fee has not been received in Allowed Files Branch as of _____

In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (f), and a verified showing as to the causes of the delay.

If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.

5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
☐ The corrected and/or substitute drawings were received on _____.
6. ☐ The reason(s) below.

 DIRECT ANY INQUIRIES TO :
 PUBLISHING DIVISION
 MARCIA CAMPBELL-JONES
 (703) 305-8190
 OR
 PRISCILLA FULLER
 (703) 305-8203.

WYETH 002-000911

PTO/SSS (11-99)

Approved for use through 10/31/99. OMB 0851-0031

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REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)



In re Application of

Sherman et al

Application Number

08/821,137

Filed

3/20/97

Group Art Unit

1502

Examiner

Huling

Paper No. 6

Assistant Commissioner for Patents
Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE)

☒ (A) referred to in United States Patent Number 6274171 column 1☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____ filed _____ on page _____ of paper number _____☐ (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____ filed _____, or☐ (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

Signature

9/25/01

Date

Typed or printed name

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Approved by: _____
(initials)

Unit: _____

WYETH 002-000912

PTO/SB/68 (04-01)

Approved for use through 10/31/2002. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

RECEIVED

DEC 05 2001

File Information Unit

In re Application of

Sherman

Application Number

08/821,137

Filed

3-20-97

Art Unit

Examiner

Spear

Paper No. #7

Assistant Commissioner for Patents
Washington, DC 20231

1. ☒ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☒ (A) referred to in:

United States Patent Application Publication No. _____, page _____, line _____.

United States Patent Number 6,274,171 B1, column FF, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

John Semikloze
Signature

Dec 5, 2001

Date

John Semikloze
Typed or printed name

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Approved by: gerUnit: F-14

WYETH 002-000913

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PTO/BB/88 (11-96)
 Approved: as through 10/31/99. OMB 0651-0031
 Patent and Trademark Office U.S. DEPARTMENT OF COMMERCE

REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)

RECEIVED

JAN 24 2002

File Information Unit

In re Application of

Application Number

Filed

08/821137

03-20-97

Group Art Unit

Examiner

1501

Huling

Paper No. 8

Assistant Commissioner for Patents
 Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE)

☒ (A) referred to in United States Patent Number 6274171, column _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____, filed _____, on page _____ of paper number _____.

☐ (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____, or

☐ (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

Shoaib Chayur
 Signature

01-24-02
 Date

Shoaib Chayur
 Typed or printed name

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Approved by

JAN 24 2002
 (Initials)

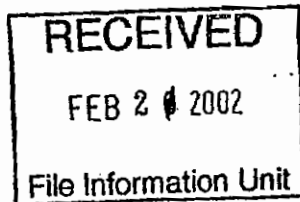
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WYETH 002-000914

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REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14



In re Application of

Application Number

File

08-821137

mar 28, 1997

Group Art Unit

Examiner

Paper No. #9

Assistant Commissioner for Patents
 Washington, DC 20231

I hereby request access under 37 CFR 1.14(e)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE)

- ☐ (A) referred to in United States Patent Number 6,274,171 column _____
- ☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e. Application No. _____, filed _____, on page _____ of paper number _____
- ☐ (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____
- ☐ (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

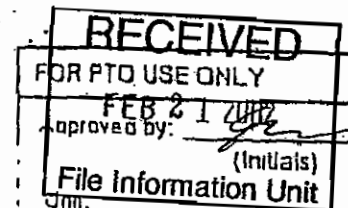
Darlene Jones

Signature

Darlene Jones

Typed or printed name

Date



WYETH 002-000915

PTO/SB/58 (04-01)

Approved for use through 10/31/2002. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

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JUN 18 2002

File Information Unit

In re Application of

Application Number

62/821137

Filed

3-20-77

Art Unit

Examiner

Paper No.

#10

Assistant Commissioner for Patents
Washington, DC 20231

1. ☒ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☒ (A) referred to in:United States Patent Application Publication No. 6279 171, page 1, line 1United States Patent Number , column , line , or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. , page , line ☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or1.14(e)(2)(i), i.e., Application No. , paper No. , page , line

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Signature

Date

Typed or printed name

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Approved by:

(initials)

Unit:

WYETH 002-000916

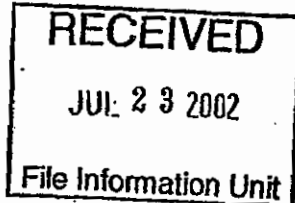
PTO/SB/68 (04-01)

Approved for use through 10/31/2002. OMA 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)



In re Application of

Application Number

08/821137

Filed

3/20/97

Art Unit

Examiner

Paper No. #11

Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:

United States Patent Application Publication No. _____, page _____, line _____.

United States Patent Number 6403120, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Signature

DAVID E. HESS

Typed or printed name

7/23/02

Date

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Approved by:

Unit: FEU-

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WYETH 002-000917

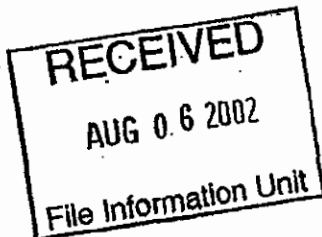
PTO/SB/65 (04-01)

Valid for use through 10/31/2002. OMB 0551-0031

U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)



In re Application of

Application Number

08-821137

Filed

3-20-97

Art Unit

Examiner

Paper No. #12Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified
☐ ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution
Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:

United States Patent Application Publication No. _____, page _____, line _____

United States Patent Number 6274171, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant
has filed an authorization to lay open the complete application to the public.

Victor Telleriu
Signature

8-6-02

Date

Victor Telleriu
Typed or printed name

FOR PTO USE ONLY

Approved by: gm

(Initials)

Unit: PRU

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20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

WYETH 002-000918

PTO/SB/88 (04-01)

Approved for use through 10/31/2002. OMB 0651-0031

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

In re Application of

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SEP 27 2002

File Information Unit

Application Number

08-821137

Filed

3 20 97

Art Unit

Examiner

Paper No. #13

Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:

United States Patent Application Publication No. _____, page _____, line _____,

United States Patent Number 6274171, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Moe Johnson

Signature

9 27 02

Date

MOE JOHNSON

Typed or printed name

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Unk. File Information Unit (Initials)

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WYETH 002-000919

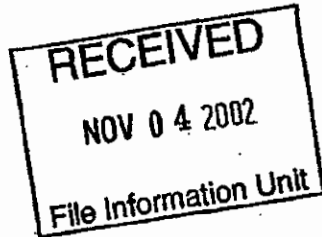
PTO/SB/68 (04-01)

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)



In re Application of

Application Number

08/821137

Filed

mar 20, 1997

Art Unit

1501

Examiner

Halmg

Paper No. 19

Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:United States Patent Application Publication No. 6419958, page _____, line _____.

United States Patent Number _____, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Darlene Innes

Signature

Darlene Innes

Typed or printed name

Date

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(Initials)

Unit: _____

WYETH 002-000920

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PTO/SB/68 (11-96)
 Patent and Trademark for use through 10/31/1999. CMB 0651-0031
 Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(A)

RECEIVED DEC 09 2002 File Information Unit Assistant Commissioner for Patents Washington, DC 20231	In re Application of Sherman, et al	
	Application Number 08/821,137	Filed 3/20/97
	Group Art Unit 1501	Examiner Hu/ing
		Paper No. 15

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above identified ABANDONED application, which is: (CHECK ONE)

- ☒ (A) referred to in United States Patent Number **6,274,171**, column ____.
- ☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____, filed _____, on page _____ of paper number _____.
- ☐ (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____, or
- ☐ (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

Cantwell and Paxton, Inc. Signature Type or Printed Name	12-9-02
	Date
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	Unit: _____

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WYETH 002-000921

2-22C

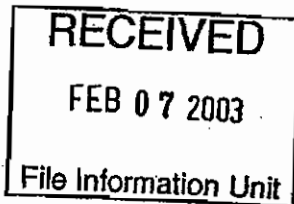
PTO/SB/68 (04-01)

Approved for use through 10/31/2002, OMB 0651-0031

U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)



In re Application of

Sherman et al

Application Number

08/821,137

Filed

3/20/97

Art Unit

Examiner

Paper No.

#16

Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:

United States Patent Application Publication No. 6224171, page _____, line _____,

United States Patent Number _____, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Nancy Perry
Signature

2/7/03
Date

Nancy Perry
Typed or printed name

FOR PTO USE ONLY

Approved by: _____

(Initials)

Unit: _____

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

WYETH 002-000922

PTO/S2/68 (04-01)

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

RECEIVED

MAR 11 2003

File Information Unit

In re Application of

Sherman

Application Number

08/821137

Filed

3/20/97

Art Unit

Examiner

Paper No.

#17

Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:United States Patent Application Publication No. 6274171, page _____, line _____.

United States Patent Number _____, column _____, line _____, or

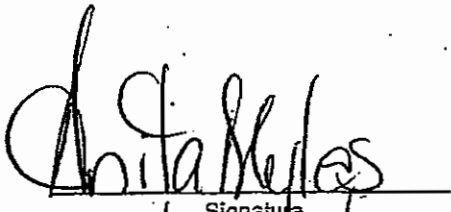
an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

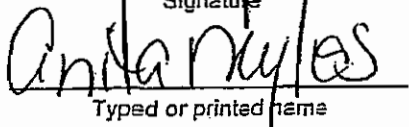
☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.


2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.



Signature



Typed or printed name



Date

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Approved by: MAR 11 2003

(initials)

Unit:

File Information Unit

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WYETH 002-000923

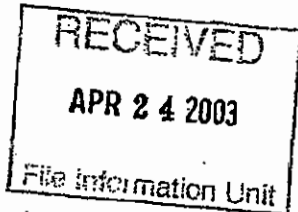
4-125B

PTO/SB/53 (04-01)

Approved for use through 10/31/2002. OMB 0551-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)



In re Application of <i>Sherman</i>	
Application Number <i>08/821137</i>	Filed <i>3/20/97</i>
Art Unit	Examiner

Paper No. *18*Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:United States Patent Application Publication No. *6274171*, page _____, line _____,

United States Patent Number _____, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Anda Nyles
Signature
Anda Nyles
Typed or printed name

4/24/03
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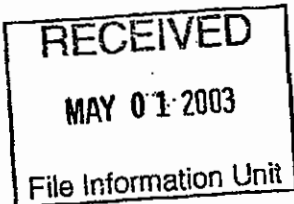
WYETH 002-000924

PTO/SB/68 (04-01)

Approved for use through 10/31/2002. OMB 0651-0031

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

In re Application of

Sherman et al

Application Number

08/821,137

Filed

3/20/97

Art Unit

Examiner

Paper No. *#19*Assistant Commissioner for Patents
Washington, DC 20231

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☒ (A) referred to in:

United States Patent Application Publication No. _____, page _____, line _____.

United States Patent Number *6274171*, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

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WYETH 002-000925



US006274171B1

(12) **United States Patent**
Sherman et al.

(10) Patent No.: **US 6,274,171 B1**
 (45) Date of Patent: **Aug. 14, 2001**

(54) **EXTENDED RELEASE FORMULATION OF
 VENLAFAXINE HYDROCHLORIDE**

(75) Inventors: Deborah M. Sherman, Plattsburgh;
 John C. Clark, Peru, both of NY (US);
 John U. Lamer, St. Albans, VT (US);
 Steven A. White, Champlain, NY (US)

(73) Assignee: American Home Products
 Corporation, Madison, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this
 patent is extended or adjusted under 35
 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 09/488,629

(22) Filed: Jan. 20, 2000

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/964,328, filed on
 Nov. 5, 1997, now abandoned, which is a continuation-in-
 part of application No. 08/821,137, filed on Mar. 20, 1997,
 now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25,
 1996.

(51) Int. Cl.⁷ A61K 9/52; A61K 9/54;
 A61K 9/62

(52) U.S. Cl. 424/461; 424/457; 424/458;
 424/459; 514/781; 514/962

(58) Field of Search 424/495, 494,
 424/461, 458, 459, 457, 456, 462

(56) **References Cited**

U.S. PATENT DOCUMENTS

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 0667150 1/1995 (EP) .
 0797991 10/1997 (EP) .
 9427589 12/1994 (WO) .
 9737640 10/1997 (WO) .

* cited by examiner

Primary Examiner—James M. Spear

(74) Attorney, Agent, or Firm—Rebecca R. Barrett

(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage
 formulation and unit dosage form thereof of venlafaxine
 hydrochloride, an antidepressant, which provides better con-
 trol of blood plasma levels than conventional tablet formu-
 lations which must be administered two or more times a day
 and further provides a lower incidence of nausea and vom-
 iting than the conventional tablets. More particularly, the
 invention comprises an extended release formulation of
 venlafaxine hydrochloride comprising a therapeutically
 effective amount of venlafaxine hydrochloride in spheroids
 comprised of venlafaxine hydrochloride, microcrystalline
 cellulose and, optionally, hydroxypropylmethylcellulose
 coated with a mixture of ethyl cellulose and hydroxypropyl-
 methylcellulose.

25 Claims, No Drawings

WYETH 002-000926

3/28/07/28/97

WYETH 002-000927

STAPLE AREA

★ U.S. GOVERNMENT PRINTING OFFICE: 1997-424-353

PATENT NUMBER

ORIGINAL CLASSIFICATION

CLASS

SUBCLASS

424

456

APPLICATION SERIAL NUMBER

08/821,137

CROSS REFERENCE(S)

CLASS

SUBCLASS

(ONE SUBCLASS PER BLOCK)

APPLICANT'S NAME (PLEASE PRINT)

424

457

458

461

Sherman

IF REISSUE, ORIGINAL PATENT NUMBER

INTERNATIONAL CLASSIFICATION

A61K

9/58

GROUP
ART UNIT

ASSISTANT EXAMINER (PLEASE STAMP OR PRINT FULL NAME)

Amy Hulna

PRIMARY EXAMINER (PLEASE STAMP OR PRINT FULL NAME)

Primary Examiner

Group 1500

PTO 270
(REV. 5-91)

ISSUE CLASSIFICATION SLIP

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PATENT AND TRADEMARK OFFICE

WYETH 002-000928

POSITION	ID NO.	DATE
CLASSIFIER	12	5/2/97
EXAMINER	8/3	7/3/97
TYPIST		
VERIFIER		
CORPS CORR.		
SPEC. HAND		
FILE MAINT.		
DRAFTING		

INDEX OF CLAIMS

Claim	Date
Final Original	
1	9/1/97
2	11/1/97
3	11/1/97
4	11/1/97
5	11/1/97
6	11/1/97
7	11/1/97
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SYMBOLS

✓ Rejected

○ Allowed

— (Through number)

— Cancelled

— Restricted

— Non-elected

— Interference

A Appeal

O Objected

Claim	Date
Final Original	
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WYETH 002-000929

SEARCHED			
Class	Sub.	Date	Exmr.
424 ↓	458 461 457	7/97	act

SEARCH NOTES		
none	Date	Exmr.
	7/97	act

INTERFERENCE SEARCHED			
Class	Sub.	Date	Exmr.
424 ↓	456 458 457 461	7/97	act

WYETH 002-000930

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 1996

Application or Docket Number

08/821137

CLAIMS AS FILED - PART I

(Column 1)

(Column 2)

SMALL ENTITY

OR

OTHER THAN
SMALL ENTITY

FOR	NUMBER FILED	NUMBER EXTRA
BASIC FEE		
TOTAL CLAIMS	10 minus 20 = *	0
INDEPENDENT CLAIMS	5 minus 3 = *	2
MULTIPLE DEPENDENT CLAIM PRESENT		

RATE	FEE
	385.00
x\$11=	
x40=	
+130=	
TOTAL	

RATE	FEE
	770.00
x\$22=	
x80=	160
+260=	
TOTAL	930

* If the difference in column 1 is less than zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

(Column 1)

(Column 2)

(Column 3)

SMALL ENTITY

OR

OTHER THAN
SMALL ENTITY

AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus **	=
Independent	*	Minus ***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM			

RATE	ADDI- TIONAL FEE
x\$11=	
x40=	
+130=	
TOTAL ADDIT. FEE	

RATE	ADDI- TIONAL FEE
x\$22=	
x80=	
+260=	
TOTAL ADDIT. FEE	

AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
Total	*	Minus **	=
Independent	*	Minus ***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM			

RATE	ADDI- TIONAL FEE
x\$11=	
x40=	
+130=	
TOTAL ADDIT. FEE	

RATE	ADDI- TIONAL FEE
x\$22=	
x80=	
+260=	
TOTAL ADDIT. FEE	

AMENDMENT C	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
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Independent	*	Minus ***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM			

RATE	ADDI- TIONAL FEE
x\$11=	
x40=	
+130=	
TOTAL ADDIT. FEE	

RATE	ADDI- TIONAL FEE
x\$22=	
x80=	
+260=	
TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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1ST EXAMINER	Theresa RKO	DATE	7/3/97
2ND EXAMINER		DATE	

WYETH 002-000932

APPLICATION NUMBER		TYPE APPL		FILING DATE			SPECIAL HANDLING		GROUP ART UNIT		CLASS		SHEETS OF DRAWING	
M/821137		1		032097			0		1502		424		— — —	
TOTAL CLAIMS		INDEPENDENT CLAIMS		SMALL ENTITY?		FILING FEE		FOREIGN LICENSE		ATTORNEY DOCKET NUMBER				
110		5		0		930		7		440-95011				

CONT STATUS		PARENT APPLICATION						PCT APPLICATION SERIAL NUMBER						PARENT PATENT NUMBER						DATE		
CODE	SERIAL NUMBER																			MONTH	DAY	YEAR
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PATENT APPLICATION

07821137



08821137

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INITIALS MAY 02 97 45

Date
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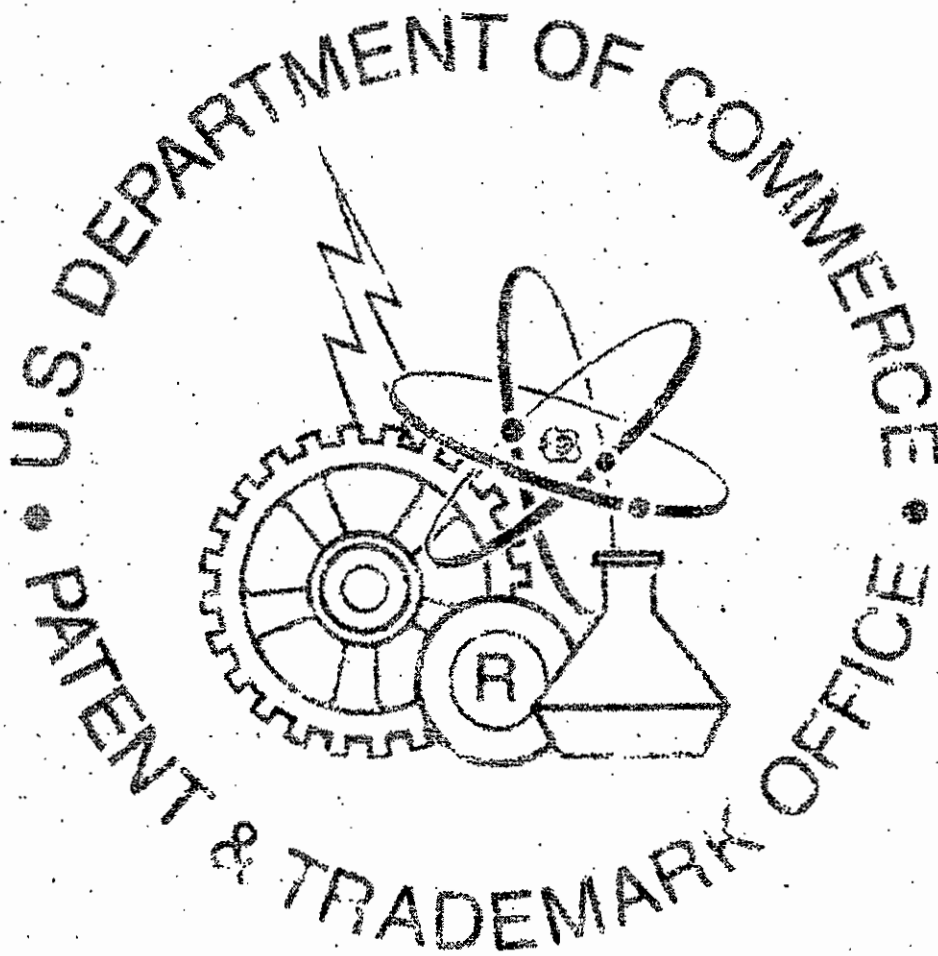
CONTENTS

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Date Received
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1	Application <i>D.S.</i> papers	0730-27
2	Interview Summary	8/5/97
3	Ex. Audit / A	8/5/97
4	IDS	7-14-97
5	ABANDONED	FEB -3 1998
6	Request for Access	9-25-9
7	Request for Access	12-5-01
8	Request for Access	1-24-02
9	Request for Access	2/21/02
10	Request for Access	6/8/02
11	Request for Access	7/23/02
12	Request for Access	8/6/02
13	Request for Access	9/27/02
14	Request for Access	11/4/02
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16	Request for Access	2/7/03
17	Request for Access	3-1-03
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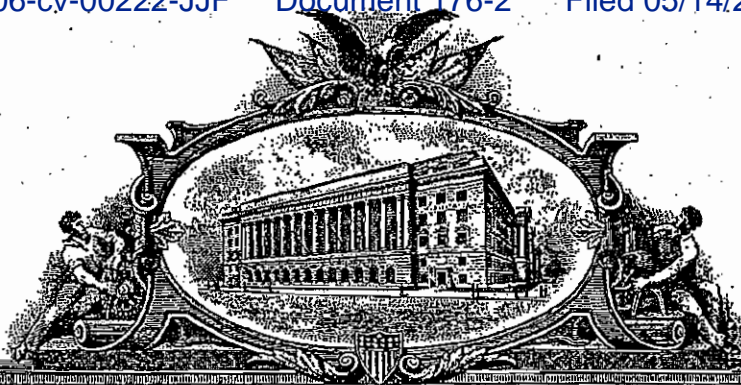
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FILING DATE: November 05, 1997

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L. EDELEN
Certifying Officer

WYETH 002-000563

UTILITY SERIAL NUMBER	PATENT DATE	PATENT NUMBER	DECLINED
SERIAL NUMBER 08/964,328	FILING DATE 11/05/97	CLASS 424	SUBCLASS 465
GROUP ART UNIT 1615		EXAMINER SPEAR	

DEBORAH MARIE SHERMAN, PLATTSBURGH, NY; JOHN CLIFTON CLARK, PERU, NY;
JOHN ULRICK LAMER, ST. ALBANS, VT.

CONTINUING DATA***

VERIFIED THIS APPLN IS A CIP OF 08/821,137 03/20/97 ABN
PROVISIONAL APPLICATION NO. 60/014,006 03/25/96

FOREIGN APPLICATIONS***

VERIFIED

FOREIGN FILING LICENSE GRANTED 02/20/98

Foreign priority claimed 35 USC 119 conditions met	<input type="checkbox"/> yes <input checked="" type="checkbox"/> no	AS FILED	STATE OR COUNTRY NY	SHEETS DRWGS. 0	TOTAL CLAIMS 18	INDER. CLAIMS 4	FILING FEE RECEIVED \$1,002.00	ATTORNEY'S DOCKET NO. AHP-95011-1-
Verified and Acknowledged		Examiner's initials						

RONALD W ALICE
AMERICAN HOME PRODUCTS CORPORATION
PATENT LAW DEPARTMENT
ONE CAMPUS DRIVE
PARSIPPANY NJ 07054

EXTENDED RELEASE FORMULATION

TITLE *Venlafaxine Extended Release Formulations*

U.S. DEPT. OF COMM./PAT. & TM—PTO-436L (Rev. 12-94)

PARTS OF APPLICATION FILED SEPARATELY		Applications Examiner	
NOTICE OF ALLOWANCE MAILED		CLAIMS ALLOWED	
Amount Due		Total Claims	Print Claim
Date Paid	Assistant Examiner	DRAWING	
Issue Fee		Sheets Drawn	Files Drawn
Label Area		Primary Examiner	
PREPARED FOR ISSUE		ISSUE BATCH NUMBER	
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NOTE: PTO-436L
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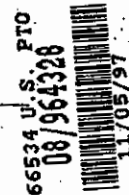
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Case Docket No. AHP-95011-1-C1
 PATENT



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 Washington, D.C. 20231

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Transmitted herewith for filing is the patent application of

Inventor: Deborah M. Sherman, John Clifton Clark, John Ulrick Lamar

For: Extended Release Formulation

Enclosed are:

- ☐ _____ sheets of drawing.
- ☐ An assignment of the invention to _____
- ☐ A certified copy of a _____ application.
- ☐ Associate power of attorney.

CLAIMS AS FILED				
(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) BASIC FEE \$790.00
TOTAL CLAIMS	18 -20 =	0	x \$22.00	0.00
INDEPENDENT CLAIMS	5 -3 =	2	x \$82.00	164.00
MULTIPLE DEPENDENT CLAIMS	0	0	\$270.00	0.00
TOTAL FILING FEE →				954.00

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- ☐ A check in the amount of _____ to cover the filing fee is enclosed.
- ☒ This application is a continuation-in-part under 37 CFR 1.53(b)
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 which, in turn, claims priority from Provisional Application
 No. 60/014,006 filed March 25, 1996.

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Case Docket No. AHP-95011-1-C1
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ASSISTANT COMMISSIONER FOR PATENTS
 Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application of

Inventor: Deborah M. Sherman, John Clifton Clark, John Ulrick Lamar

For: Extended Release Formulation

Enclosed are:

- ☐ _____ sheets of drawing.
- ☐ An assignment of the invention to _____
- ☐ A certified copy of a _____ application.
- ☐ Associate power of attorney.

CLAIMS AS FILED				
(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) BASIC FEE \$790.00
TOTAL CLAIMS	18 -20 =	0	x \$22.00	0.00
INDEPENDENT CLAIMS	5 -3 =	2	x \$82.00	164.00
MULTIPLE DEPENDENT CLAIMS	0	0	\$270.00	0.00
TOTAL FILING FEE				954.00

- ☒ Please charge my Deposit Account No. 01-1425 in the amount of \$ 954.00. Two additional copies of this sheet are enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of the application to Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.
- ☐ A check in the amount of _____ to cover the filing fee is enclosed.
- ☒ This application is a continuation-in-part under 37 CFR 1.53(b) of copending Application No. 08/821,137, filed March 20, 1997, which, in turn, claims priority from Provisional Application No. 60/014,006 filed March 25, 1996.

Arthur G. Seifert
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 Reg. No. 28,040

FORM PO-1082 (11-69)

USCOMM-DC 60424-P69

N2769 L (9/96)

WYETH 002-000566

66534 U.S. PTO

08/964328



11/05/97

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

01/15/1998 HGD/BDH 00000021 DA# 011425 08964328
01 FC:101 790.00 CH
02 FC:102 82.00 CH

PTO-1556
(5/87)

WYETH 002-000567

AHP-95011-1-CI
PATENT

-16-

ABSTRACT

EXTENDED RELEASE FORMULATION

5 This invention relates to a 24 hour extended release dosage formulation and unit
dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides
better control of blood plasma levels than conventional tablet formulations which must
be administered two or more times a day and further provides a lower incidence of
nausea and vomiting than the conventional tablets,

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WYETH 002-000568

HP-95011-1-C1
PATENT

-1-

EXTENDED RELEASE FORMULATION

This application is a continuation -in-part of copending Application No. 08/821,137, filed March 20, 1997, which, in turn, claims priority from Provisional
5 Application No. 60/014,006 filed March 25, 1996.

Background of the Invention

Extended release drug formulations are conventionally produced as compressed
10 tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration
15 from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/antiinflammatory drug etodolac
20 (Lodine®) appears in US patent 4,966,768. US patent 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug
25 industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders
30 of drug/matrix are extruded, chopped into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. Gelatin capsules are filled with the film-coated spheroids in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a gelatin capsule to obtain
35 desired release rates and blood levels. US patent 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propranolol in admixture with microcrystalline cellulose

WYETH 002-000569

IP-95011-1-C1
PATENT

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wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in US patent 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

Brief Description of the Invention

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours.

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Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

Detailed Description of the Invention

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent

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venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101),
5 about one half percent hydroxypropyl methylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19-24% and a hydroxypropoxy content of 4-13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10
10 to 20 percent hydroxypropyl methylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0-51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12%. The ethyl cellulose used herein is Aqualon
15 HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable
20 hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2-5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was
25 generally 50-55°C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets
30 were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70% dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of
35 microcrystalline cellulose and hydroxypropyl methylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone,

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methycellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

Example 1.

VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES

A mixture of 44.8 parts (88.4 % free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropyl methylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into hard gelatin capsules conventionally.

Example 2.

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

Example 3.

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

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Example 4.

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1-4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethyl cellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5 % (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6 % (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide,

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after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

Table 1

Acceptable Coated Spheroid Dissolution Rates

<u>Time (hours)</u>	<u>Average % Venlafaxine HCl released</u>
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into hard gelatin capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

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The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

5 where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

10 Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to
15 the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

[Text continues with Table 2 on next page]

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Table 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 x 75 mg (ER)capsules (q 24 hr)	1 x 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

5

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

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Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate

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release tablets given 12 hours apart. The peak level of venlafaxine from (ER) , somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

Table 3.

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

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The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20°C until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 µL of a stock internal standard solution (150 µg/mL). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 µL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 µL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm x 4.6 mm, 5 µ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

Thus, the desired dissolution rate of a sustained release dosage form of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

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What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a hard gelatin capsule containing a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation according to claim 1 wherein the spheroids are comprised of about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

3. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

	<u>Time (hours)</u>	<u>Average % Venlafaxine HCl released</u>
	2	<30
	4	30-55
	8	55-80
	12	65-90
	24	>80

4. An extended release formulation according to claim 2 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62% by weight of microcrystalline cellulose.

5. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

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6. A composition according to claim 2 wherein the film coating comprises 6- 8% by weight of total weight.

7. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

8. A composition according to claim 2 wherein film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

9. A film coating composition according to claim 7 which is comprised of about 85% by total weight of film coating of ethyl cellulose having a 44.0-51.0% content of ethoxy groups, and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

10. A film coating composition according to claim 7 which is comprised of 85% by weight of ethyl cellulose type HG 2834 and 15% by weight of hydroxypropylmethylcellulose type 2910.

11. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 85% ethyl cellulose type HG 2834 and 15% hydroxypropyl-methylcellulose type 2910 sufficient to give coated spheroids having a dissolution profile which gives the desired release rate over a 24 hour period.

12. An extended release formulation of venlafaxine hydrochloride according to claim 7 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

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13. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

14. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

15

Sub A4 15. An extended release formulation according to claim 1 wherein the spheroids are comprised of about 6% to 40% venlafaxine hydrochloride by weight, about 50% to about 940% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

16. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 15 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

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17. An extended release formulation according to claim 14 wherein the spheroids are composed of about 8.25% by weight of venlafaxine hydrochloride and about 91.75% by weight of microcrystalline cellulose, with a coating of from 3 to 5 % by weight of the total weight.
18. An extended release formulation according to claim 14 wherein the spheroids are composed of about 16.5% by weight of venlafaxine hydrochloride and about 83.5% by weight of microcrystalline cellulose, with a coating of from 4 to 6 % by weight of the total weight.

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DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **EXTENDED RELEASE FORMULATION**, the specification of which is attached hereto unless the following box is checked:

☐ was filed on _____ as United States Application Number or PCT Application Number _____ and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

NONE			Priority Claimed
(Number)	(Country)	(Day/Month/Year Filed)	<input type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under Title 35 United States Code, §119(e) of any United States Provisional application(s) listed below.

60/014,006	3/25/96
(Application Number)	(Filing Date)
_____	_____
(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

08/821,137	3/20/97	pending
(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)
_____	_____	_____

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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0232/0224

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02/24/98

NOTICE TO FILE MISSING PARTS OF APPLICATION
Filing Date Granted

An Application Number and Filing Date have been assigned to this application. However, the items indicated below are missing. The required items and fees identified below must be timely submitted ALONG WITH THE PAYMENT OF A SURCHARGE for items 1 and 2 only of \$ 120 for a ☒ large entity ☐ small entity in compliance with 37 CFR 1.27. The surcharge is set forth in 37 CFR 1.16(e). Applicant is given TWO MONTHS FROM THE DATE OF THIS NOTICE within which to file all required items and pay any fees required above to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

If all required items on this form are filed within the period set above, the total amount owed by applicant as a ☒ large entity ☐ small entity (verified statement filed); is \$ 120.

☒ 1. The statutory basic filing fee is:

- ☐ missing.
☐ insufficient.

Applicant must submit \$ _____ to complete the basic filing fee and/or file a verified small entity statement claiming such status (37 CFR 1.27).

☒ 2. Additional claim fees of \$ _____, including any multiple dependent claim fees, are required.

Applicant must either submit the additional claim fees or cancel additional claims for which fees are due.

☒ 3. The oath or declaration:

- ☐ is missing.
☐ does not cover the newly submitted items.
☐ does not identify the application to which it applies.
☐ does not include the city and state or foreign country of applicant's residence.

An oath or declaration in compliance with 37 CFR 1.63, including residence information and identifying the application by the above Application Number and Filing Date is required.

☒ 4. The signature(s) to the oath or declaration is/are:

- ☒ missing.
☐ by a person other than inventor or person qualified under 37 CFR 1.42, 1.43, or 1.47.

A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.

☒ 5. The signature of the following joint inventor(s) is missing from the oath or declaration:

An oath or declaration listing the names of all inventors and signed by the omitted inventor(s), identifying this application by the above Application Number and Filing Date, is required.

☒ 6. A \$ _____ processing fee is required since your check was returned without payment (37 CFR 1.21(m)).

☒ 7. Your filing receipt was mailed in error because your check was returned without payment.

☒ 8. The application does not comply with the Sequence Rules.
See attached "Notice to Comply with Sequence Rules 37 CFR 1.821-1.825."

☒ 9. OTHER:

Direct the response and any questions about this notice to "Attention: Box Missing Parts."

A copy of this notice MUST be returned with the response.

Customer Service Center
Initial Patent Examination Division (703) 308-1202

WYETH 002-000586

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING
DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS
FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO:
COMMISSIONER OF PATENTS AND TRADEMARKS,
WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

AHP-95011-1-C1
PATENT

#3



Arthur G. Seifert
DATE March 23, 1998

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman, John C. Clark, John U. Lamer

Serial No.: 08/964,328

Examiner:

Filed: November 5, 1997

Group No.:

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, DC 20231

**LETTER TRANSMITTING
ORIGINAL DECLARATION UNDER 37 CFR 1.63
AND PAYMENT OR SURCHARGE UNDER 37 CFR 1.16**

Sir:

This is in reply to the Notice to File Missing Parts of Application mailed February 24, 1998.

Enclosed herewith is the original executed Declaration and Power of Attorney for the above application.

Please charge the large entity surcharge of \$130 to Deposit Account 01-1425 as well as any additional required fee or credit.

Two additional copies of this letter are attached.

Respectfully submitted,

Arthur G. Seifert

Arthur G. Seifert
Attorney for Applicant
Reg. No. 28,040

Dated: March 23, 1998
Telephone: (610) 902-2627

WYETH 002-000587

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING
DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS
FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO:
COMMISSIONER OF PATENTS AND TRADEMARKS,
WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

#3
AHP-95011-1-C1
PATENT



Arthur G. Seifert
DATE March 23, 1998

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman, John C. Clark, John U. Lamer

Serial No.: 08/964,328

Examiner:

Filed: November 5, 1997

Group No.:

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, DC 20231

**LETTER TRANSMITTING
ORIGINAL DECLARATION UNDER 37 CFR 1.63
AND PAYMENT OR SURCHARGE UNDER 37 CFR 1.16**

Sir:

This is in reply to the Notice to File Missing Parts of Application mailed February 24, 1998.

Enclosed herewith is the original executed Declaration and Power of Attorney for the above application.

Please charge the large entity surcharge of \$130 to Deposit Account 01-1425 as well as any additional required fee or credit.

Two additional copies of this letter are attached.

Respectfully submitted,

Arthur G. Seifert

Arthur G. Seifert
Attorney for Applicant
Reg. No. 28,040

Dated: March 23, 1998
Telephone: (610) 902-2627

WYETH 002-000588



#3
AHP-95011-1-C1
PATENT

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled _____

the specification of which _____

(check one) _____ is attached hereto.

X was filed on November 5, 1997 as
Application Serial No. 08/964,328
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Priority Claimed
Yes No

NONE
(Number) (Country) (Day/Month/Year Filed)

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States Provisional Application(s) for Patent listed below:

60/014,006 3/25/96
(Provisional Appln. No.) (Filing Date)

(Provisional Appln. No.) (Filing Date)

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

08/821,137 3/20/97 Abandoned
(Application Serial No.) (Filing Date) (Status - Patented, pending, abandoned)

(Application Serial No.) (Filing Date) (Status - Patented, pending, abandoned)

AHP-95011-1-C1
PATENT

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Egon E. Berg, Reg. No. 21,117; Ronald W. Alice, Reg. No. 27,609; Thomas J. DesRosier, Reg. No. 30,168; all of One Campus Drive, Parsippany, New Jersey, 07054; and Rebecca R. Barrett, Reg. No. 35,152; Steven R. Eck, Reg. No. 36,126; Arnold S. Milowsky, Reg. No. 35,288; Michael R. Nagy, Reg. No. 33,432; Arthur G. Seifert, Reg. No. 28,040; George Tarnowski, Reg. No. 27,472; all of P.O. Box 8299, Philadelphia, Pennsylvania, 19101; Robert F. Boswell, Jr., Reg. No. 35,072, of P. O. Box 26609, Richmond, Virginia, 23261-6609; and Daniel B. Moran, Reg. No. 41,204 of 401 N. Middletown Road, Pearl River, New York, 10965.

Address all telephone calls to Arthur G. Seifert at
telephone number (610) 902-2627

Address all correspondence to Ronald W. Alice, American Home Products Corporation, Patent Law Department - 2B, One Campus Drive, Parsippany, New Jersey, 07054.

Full name of sole or first inventor Deborah Marie Sherman
Inventor's signature *Deborah Marie Sherman* 12 Mar 98
Date
Residence 5 Belmont Avenue, Plattsburgh, New York 12901
Citizenship United States of America
Post Office Address Same as residence

Full name of second joint inventor, if any John Clifton Clark
Inventor's signature *John Clifton Clark* 16 Mar 98
Date
Residence 1 Rounds Drive, Peru, New York 12972
Citizenship United States of America
Post Office Address Same as Residence

Full name of third joint inventor, if any John Ulrich Lamer
Inventor's signature *John Ulrich Lamer* 16 Mar 98
Date
Residence 22 Farrar Street, St. Albans, Vermont 05478
Citizenship United States of America
Post Office Address Same as Residence



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
 Washington, D.C. 20231

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO./TITLE
--------------------	---------------------	-----------------------	---------------------------

08/964,328 11/05/97 SHERMAN D AHP-95011-1-

0232/0224

RONALD W ALICE
 AMERICAN HOME PRODUCTS CORPORATION
 PATENT LAW DEPARTMENT
 ONE CAMPUS DRIVE
 PARSIPPANY NJ 07054

NOT ASSIGNED

DATE MAILED: 1615

02/24/98

NOTICE TO FILE MISSING PARTS OF APPLICATION
Filing Date Granted

An Application Number and Filing Date have been assigned to this application. However, the items indicated below are missing. The required items and fees identified below must be timely submitted **ALONG WITH THE PAYMENT OF A SURCHARGE** for items 1 and 3-6 only of \$ 130 for a ☒ large entity ☐ small entity in compliance with 37 CFR 1.27. The surcharge is set forth in 37 CFR 1.16(e). Applicant is given **TWO MONTHS FROM THE DATE OF THIS NOTICE** within which to file all required items and pay any fees required above to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

If all required items on this form are filed within the period set above, the total amount owed by applicant as a ☒ large entity ☐ small entity (verified statement filed), is \$ 130.

- ☐ 1. The statutory basic filing fee is:

- ☐ missing.
☐ insufficient.

Applicant must submit \$ _____ to complete the basic filing fee and/or file a verified small entity statement claiming such status (37 CFR 1.27).

- ☐ 2. Additional claim fees of \$ _____, including any multiple dependent claim fees, are required. Applicant must either submit the additional claim fees or cancel additional claims for which fees are due.

- ☐ 3. The oath or declaration:

- ☐ is missing.
☐ does not cover the newly submitted items.
☐ does not identify the application to which it applies.
☐ does not include the city and state or foreign country of applicant's residence.

An oath or declaration in compliance with 37 CFR 1.63, including residence information and identifying the application by the above Application Number and Filing Date is required.

- ☒ 4. The signature(s) to the oath or declaration is/are:

- ☐ missing.
☐ by a person other than inventor or person qualified under 37 CFR 1.42, 1.43, or 1.47.

A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.

- ☐ 5. The signature of the following joint inventor(s) is missing from the oath or declaration:

An oath or declaration listing the names of all inventors and signed by the omitted inventor(s), identifying this application by the above Application Number and Filing Date, is required.

- ☐ 6. A \$ _____ processing fee is required since your check was returned without payment (37 CFR 1.21(m)).
☐ 7. Your filing receipt was mailed in error because your check was returned without payment.
☐ 8. The application does not comply with the Sequence Rules.
 See attached "Notice to Comply with Sequence Rules 37 CFR 1.821-1.825."
☐ 9. OTHER:

Direct the response and any questions about this notice to "Attention: Box Missing Parts."

A copy of this notice MUST be returned with the response.

Customer Service Center
 Initial Patent Examination Division (703) 308-1202

03/30/1998 WYLLAH 06000027 000011420 00364020
 01 PG:105 100.00 US

WYETH 002-000591



AHP-95011-1-C1
PATENT

0200

44
4/13/98

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: SHERMAN

Application No.: 08/964,328

Group Art Unit:

Filed: NOVEMBER 5, 1997

Examiner:

For: EXTENDED RELEASE FORMULATION

Assistant Commissioner for Patents
Washington, DC 20231

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT WITHIN
THREE MONTHS OF FILING OR BEFORE MAILING OF FIRST OFFICE
ACTION

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231, on the date appearing below.

Robert F. Boswell, Jr.

Robert F. Boswell, Jr.

(Typed or printed name of person mailing paper)

DATE

Feb. 9, 1998

Respectfully submitted,

Robert F. Boswell, Jr.

Robert F. Boswell, Jr.
Registration No. 35,072

Dated: *Feb. 9, 1998*

Telephone: (804)257-3613

WYETH 002-000592



AHP-95011-1-C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of **SHERMAN**

Application No.: 08/964,328

Group Art Unit:

Filed: NOVEMBER 5, 1997

Examiner:

For: EXTENDED RELEASE FORMULATION

INFORMATION DISCLOSURE STATEMENT UNDER RULE 97

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Applicants submit herewith patents, publications or other information of which they are aware, which they believe to be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 CFR 1.56. The filing of this information disclosure statement shall not be construed as a representation that a search has been made (37 CFR 1.56(g)), an admission that the information cited is, or is considered to be, material to patentability or that no other material information exists.

The filing of this information disclosure statement shall not be construed as an admission against interest in any manner. Notice of January 9, 1992, 1135 O.G. 13-25, at 25.

The references submitted are listed on the accompanying Form PTO-1449.

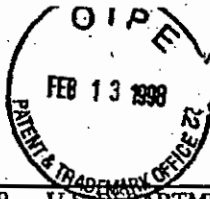
Copies of the listed patents, publications or abstracts thereof are enclosed herewith.

Respectfully submitted,

Robert F. Boswell, Jr.
Registration No. 35,072

Dated: February 9, 1998
Telephone: (804)257-3613

WYETH 002-000593

File
copy

Sheet 1 of 1

FORM PTO-1449 (REV. 2-32)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. AHP-95011-1-C1	APPLICATION NO. 08/964,328
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)		APPLICANT Sherman	
		FILING DATE November 5, 1997	GROUP <i>Au 16 15</i>

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
<i>JS</i>	3 9 5 4 9 5 9	8/27/75	Pedersen	424	21	
<i>JS</i>	4 3 6 9 1 7 2	1/18/83	Schor	424	19	
<i>JS</i>	4 1 3 8 4 7 5	2/6/79	McAinsh	424	19	
<i>JS</i>	4 3 8 9 3 9 3	6/21/83	Schor	424	19	
<i>JS</i>	4 9 6 6 7 6 8	10/30/90	Michelucci	424	468	
<i>JS</i>	5 5 0 6 2 7 0	4/9/96	Upton	514	730	
<i>JS</i>	4 5 3 5 1 8 6	8/13/86	Husbands	564	336	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER						DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
												YES	NO

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER *JAMES M. SPEAR* DATE CONSIDERED *9-27-98*

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

WYETH 002-000594

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

AHP-95011-1-C1
PATENT



DATE

Arthur G. Seifert
March 11, 1998

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Deborah M. Sherman, John C. Clark, John U. Lamer

Serial No.: 08/964,328

Group No.:

Filed: November 5, 1997

Examiner:

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, D.C. 20231

REQUEST FOR CORRECTED FILING RECEIPT

1. Attached is a copy of the official filing receipt received from the PTO in the above application for which issuance of a corrected filing receipt is respectfully requested.

2. There is an error in that the following data is:



incorrectly entered
and/or



omitted



Applicant's name



Applicant's address



Title



Filing Date



Serial Number



Foreign/PCT Application Reference



Other

RECEIVED
JUN 4 1998

in that the filing receipt should read as follows:

Third Applicant's name should read: John Ulrick Lamer

3. A. ☐ The correction is not due to any error by applicant and no fee is due.

OR

B. ☒

The correction is due to applicant's error and the fee therefor under 37 CFR 1.19(i) of \$25.00 is paid as follows:



charge Account 01-1425 \$25.00.

Dated: March 11, 1998
Telephone: (610) 971-2627

Arthur G. Seifert
Arthur G. Seifert
Reg. No. 28,040

WYETH 002-000642

DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS
FIRST CLASS MAIL IN ENVELOPE ADDRESSED TO:
COMMISSIONER OF PATENTS AND TRADEMARKS,
WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

Receipt

AHP-95011-1-C1
PATENT

#5



DATE

March 11, 1998

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Deborah M. Sherman, John C. Clark, John U. Lamer

Serial No.: 08/964,328

Group No.: 1615

Filed: November 5, 1997

Examiner: Spear

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, D.C. 20231**REQUEST FOR CORRECTED FILING RECEIPT**

1. Attached is a copy of the official filing receipt received from the PTO in the above application for which issuance of a corrected filing receipt is respectfully requested.

2. There is an error in that the following data is:



incorrectly entered
and/or



omitted



Applicant's name



Applicant's address



Title



Filing Date



Serial Number



Foreign/PCT Application Reference



Other

in that the filing receipt should read as follows:

Third Applicant's name should read: John Ulrick Lamer

3. A. ☐ The correction is not due to any error by applicant and no fee is due.

OR

B. ☒

The correction is due to applicant's error and the fee therefor under 37 CFR 1.19(i) of \$25.00 is paid as follows:



charge Account 01-1425 \$25.00.

Dated: March 11, 1998
Telephone: (610) 971-2627

Arthur G. Seifert
Reg. No. 28,040

Arthur G. Seifert

WYETH 002-000643

PTO-103X
(Rev. 8-95)

FILING RECEIPT



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
08/964,328	11/05/97	1615	\$872.00	AHP-95011-1-	0	18	4

RONALD W ALICE
AMERICAN HOME PRODUCTS CORPORATION
PATENT LAW DEPARTMENT
ONE CAMPUS DRIVE
PARSIPPANY NJ 07054

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Application Processing Division's Customer Correction Branch within 10 days of receipt. Please provide a copy of the Filing Receipt with the changes noted thereon.

Applicant(s)

DEBORAH MARIE SHERMAN, PLATTSBURGH, NY; JOHN CLIFTON
CLARK, PERU, NY; JOHN ULRICK LAMAR, ST. ALBANS, VT.

CONTINUING DATA AS CLAIMED BY APPLICANT-

THIS APPLN IS A CIP OF 08/821,137 03/20/97 ABN
PROVISIONAL APPLICATION NO. 60/014,006 03/25/96

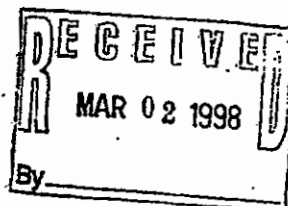
FOREIGN FILING LICENSE GRANTED 02/20/98
TITLE
EXTENDED RELEASE FORMULATION

PRELIMINARY CLASS: 424

AM. HOME PROD. CORP.

MAR 4 1998

PATENT DEPT., RADNOR



WYETH 002-000644

I HEREBY CERTIFY THAT CORRESPONDENCE IS BEING
DEPOSITED WITH THE U.S. STATES POSTAL SERVICE AS
FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO:
ASSISTANT COMMISSIONER FOR PATENTS,
WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

AHP-95011-1-C1
PATENT

Mary Ellen Fiala
DATE *August 13, 1998*



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman, John C. Clark, John U. Lamer

Serial No.: 08/964,328

Examiner:

Filed: November 5, 1997

Group: 1615

For: Extended Release Formulation

Assistant Commissioner of Patents
Washington, D.C. 20231

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR 1.97 (c) WITH FEE UNDER 37 CFR 1.17(p)

Sir:

1. The information disclosure statement transmitted herewith is being filed after three months of the filing date of this national application or the date of entry of the national stage as set forth in §1.491 in an international application or after the mailing date of the first Office action on the merits, whichever event occurred last but before the mailing date of either:

- (1) a final action under §1.113 or
- (2) a notice of allowance under §1.311,

whichever occurs first.

2. Please charge the fee under 37 CFR 1.17(p) in the amount of \$240.00 to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this application to American Home

08/19/1998 SLWS 00000000 011425 08/13/98
American Home Products Corporation Deposit Account No. 01-1425.

01 FC:126

240.00 CH

With respect to the subject matter of the above-identified application, applicants have become aware of the following references which may be material to the examination of the invention claimed:

WYETH 002-000645

AHP-95011-1-C1
PATENT

EP 0 654 264 A1

EP 0 667 150 A1

WO 94/277589

Copies of the above-cited references are enclosed herewith.

Respectfully submitted,

Arthur G. Seifert
Arthur G. Seifert
Reg. No. 28,040

Dated: August 13, 1998
Telephone: (610) 902-2627

WYETH 002-000646

DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS
FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO:
ASSISTANT COMMISSIONER FOR PATENTS,
WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

HP-95011-1-CI
PATENT

Sam 16/58
#6

Mary Ellen Fiala
DATE *August 13, 1998*



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application of: Deborah M. Sherman, John C. Clark, John U. Lamer

Serial No.: 08/964,328

Examiner:

Filed: November 5, 1997

Group: 1615

For: Extended Release Formulation

Assistant Commissioner of Patents
Washington, D.C. 20231

RECEIVED
AUG 20 PAID
GROUP 1800

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR 1.97 (c) WITH FEE UNDER 37 CFR 1.17(p)

Sir:

1. The information disclosure statement transmitted herewith is being filed after three months of the filing date of this national application or the date of entry of the national stage as set forth in §1.491 in an international application or after the mailing date of the first Office action on the merits, whichever event occurred last but before the mailing date of either:

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- (2) a notice of allowance under §1.311,

whichever occurs first.

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The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this application to American Home Products Corporation Deposit Account No. 01-1425.

With respect to the subject matter of the above-identified application, applicants have become are aware of the following references which may be material to the examination of the invention claimed:

WYETH 002-000647

AP-95011-1-C1
PATENT

EP 0 654 264 A1

EP 0 667 150 A1

WO 94/277589

Copies of the above-cited references are enclosed herewith.

Respectfully submitted,

Arthur G. Seifert

Arthur G. Seifert
Reg. No. 28,040

Dated: August 13, 1998
Telephone: (610) 902-2627

WYETH 002-000648

Sheet 1 of 1

File Copy

FORM PTO-1449 (REV. 2-32)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. AHP-95011-1-C1	SERIAL NO. 08,964,328
INFORMATION DISCLOSURE STATEMENT BY APPLICANT		APPLICANT Deborah Sherman et al.	
(Use several sheets if necessary)		FILING DATE November 5, 1998	GROUP AU 1615

U.S. PATENT DOCUMENTS

[illegible]

FOREIGN PATENT DOCUMENTS

[illegible]

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

[illegible]

EXAMINER <u>JAMES M. SPEAR</u>	DATE CONSIDERED <u>09-27-98</u>
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EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

WYETH 002-000649


UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
 Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/964,328	11/05/97	SHERMAN	D AHF-95011-1-

HM42/1014
 RONALD W ALICE
 AMERICAN HOME PRODUCTS CORPORATION
 PATENT LAW DEPARTMENT
 ONE CAMPUS DRIVE
 PARSIPPANY NJ 07054

EXAMINER

SPEAR, J

ART UNIT	PAPER NUMBER
----------	--------------

1615

DATE MAILED: 10/14/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

WYETH 002-000715

Office Action SummaryApplication No.
08/964,328

Applicant(s)

SHERMAN, ET AL.

Examiner

JAMES M. SPEAR

Group Art Unit
1615☒ Responsive to communication(s) filed on Nov 5, 1997☐ This action is FINAL.☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire THREE month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims☒ Claim(s) 1-18 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) 11, 13, and 14 is/are allowed.☒ Claim(s) 1, 15, 17, and 18 is/are rejected.☒ Claim(s) 2-10, 12, and 16 is/are objected to.☐ Claims _____ are subject to restriction or election requirement.**Application Papers**☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.☐ The drawing(s) filed on _____ is/are objected to by the Examiner.☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.☐ The specification is objected to by the Examiner.☐ The oath or declaration is objected to by the Examiner.**Priority under 35 U.S.C. § 119**☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been☐ received.☐ received in Application No. (Series Code/Serial Number) _____.☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).**Attachment(s)**☒ Notice of References Cited, PTO-892☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6☐ Interview Summary, PTO-413☐ Notice of Draftsperson's Patent Drawing Review, PTO-948☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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Art Unit: 1615

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 50 to about 70 percent micro-crystalline cellulose, does not reasonably provide enablement for 940 percent microcrystalline cellulose. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This claim appears to be a typographical error, see page 6, line 14.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Application/Control Number: 08/964,328

Page 3

Art Unit: 1615

Claims 17 and 18 recite the limitation "the spheroids" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 17 and 18 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The formulation of claims 17 and 18 improperly depends on claim 14 a method since claim 14 does not recite any limitations describing the formulation.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over McAinsh et al. US 4,138,475 in view of Wong et al. US 5,552,429.

McAinsh et al. shows a hard gelatin capsule comprised spheroids coated with a mixture of ethyl-cellulose and hydroxypropylmethyl-cellulose. The active

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Application/Control Number: 08/964,328

Page 4

Art Unit: 1615

agent propranolol is blended with micro-crystalline cellulose. See Abstract, example and claim 1. The reference does not show venlafaxine. Wong et al. is relied on for teaching extended release dosage forms comprised of the same ingredients as McAinsh et al. including the drugs venlafaxine and propranolol. See column 4, lines 7-10, column 6, lines 54-55, column 7, lines 18-22, formulation 5. To use the venlafaxine of Wong et al. in the McAinsh et al. capsule with a reasonable expectation of success would have been obvious to one of ordinary skill in the art. The motivation being a desire to obtain optimum drug efficacy over a prolonged period of time while improving patient compliance by reducing the number of dosages required.

Claims 2-10, 12 and 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 11, 13 and 14 are allowed.

Claims 1, 15, 17 and 18 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner James M. Spear whose telephone

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Application/Control Number: 08/964,328

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number is (703) 308-2457. The examiner can normally be reached on Monday through Friday from 6:30 AM to 12:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3592 or (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

SPEAR; aco

October 5, 1998

James M. Spear
PATENT EXAMINER
ART UNIT 1615

WYETH 002-000720

Notice of References CitedApplication No.
08/964,328

Applicant(s)

SHERMAN, ET AL.

Examiner

JAMES M. SPEAR

Group Art Unit

1615

Page 1 of 1

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
A	5,552,429	09/03/96	WONG, ET AL.	514	415
B					
C					
D					
E					
F					
G					
H					
I					
J					
K					
L					
M					

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
N						
O						
P						
Q						
R						
S						
T						

NON-PATENT DOCUMENTS

	DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
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I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231



**U.S. DEPARTMENT OF COMMERCE
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Washington, D.C. 20231

DATE

Arthur G. Seifert
April 13, 1997

Docket No. AHP-95011-1-C1

In re Patent Application of Deborah M. Sherman, John C. Clark, John U. Lamar

Serial No. 08/964,328

Examiner Spear, J.

Filed November 5, 1997

Group 1615

For Extended Release Formulation



ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

☐ No additional fee is required.

The fee has been calculated as shown below.

CLAIMS AS AMENDED						
(1)	(2) CLAIMS REMAINING AFTER AMENDMENT	(3)	(4) HIGHEST NO. PREVIOUSLY PAID FOR	(5) PRESENT EXTRA	(6) RATE	(7) ADDITIONAL FEE
TOTAL CLAIMS	25	MINUS	20	5	x \$18.	90.00
INDEP. CLAIMS	6	MINUS	5	1	x \$78.	78.00
MULTIPLE DEPENDENT CLAIMS	0		0	0	\$260.	168.00
				TOTAL ADDITIONAL FEE FOR THIS AMENDMENT →		

- * If the entry in Column 2 is less than the entry in Column 4, write "0" in Column 5.
 ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
 *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

☐ Fee for Terminal Disclaimer under 37CFR 1.20 (d) (\$110.00) is also transmitted herewith.

☒ Fee of \$ 870.00 pursuant to 37 CFR 1.17(a) for extension of time under 37 CFR 1.136(a) is also transmitted herewith. (3 mos. extension)

☒ Charge \$ 1,038.00 to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

☒ The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required by this paper to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

Arthur G. Seifert
Arthur G. Seifert
Reg. No. 28,040

WYETH 002-000732

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AND TRADEMARKS
Washington, D.C. 20231

DATE

April 13, 1999

Docket No. AHP-95011-1-C1

In re Patent Application of Deborah M. Sherman, John C. Clark, John U. Lamar

Serial No. 08/964,328

Examiner Spear, J.

Filed November 5, 1997

Group 1615

For Extended Release Formulation



ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

APR 21 1999

GROUP 18

Sir:

Transmitted herewith is an amendment in the above-identified application.

☐ No additional fee is required.

The fee has been calculated as shown below.

CLAIMS AS AMENDED						
(1)	(2) CLAIMS REMAINING AFTER AMENDMENT	(3)	(4) HIGHEST NO. PREVIOUSLY PAID FOR	(5) PRESENT EXTRA	(6) RATE	(7) ADDITIONAL FEE
TOTAL CLAIMS	25	MINUS	20	5	x \$18.	90.00
INDEP. CLAIMS	6	MINUS	5	1	x \$78.	78.00
MULTIPLE DEPENDENT CLAIMS	0		0	0	\$260.	168.00
				TOTAL ADDITIONAL FEE FOR THIS AMENDMENT		

- * If the entry in Column 2 is less than the entry in Column 4, write "0" in Column 5.
 ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
 *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

- ☐ Fee for Terminal Disclaimer under 37CFR 1.20 (d) (\$110.00) is also transmitted herewith.
- ☒ Fee of \$ 870.00 pursuant to 37 CFR 1.17(a) for extension of time under 37 CFR 1.136(a) is also transmitted herewith. (3 mos. extension)
- ☒ Charge \$ 1,038.00 to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required by this paper to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

Arthur G. Seifert
Arthur G. Seifert
Reg. No. 28,040

WYETH 002-000733

AHP-95011-1-C1
Patent

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WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

DATE

William S. Leppard
April 13, 1999

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of: Deborah M. Sherman, John C. Clark, John U. Lamar

Serial No.: 08/964,328

Examiner: Spear, J.

Filed: November 5, 1997

Group: 1615

For: Extended Release Formulations

Assistant Commissioner for Patents
Washington, D.C. 20231

8/17
L.M.
4-22-99

REPLY UNDER RULE 111 WITH
AMENDMENT UNDER RULE 115

Sir:

Pending claims 1-18 were examined in the Office Action dated October 14, 1999. Claims 11, 13 and 14 are allowed. Claims 1 is rejected under 35 USC 103 as being obvious. Dependent claims 2 -10, 12 and 16 are objected to as being based upon the rejected claim 1. Claim 15 is rejected under 35 USC 112, paragraph two, with respect to the typographical error "940%". Claims 17 and 18 are objected to as being improperly dependent upon claim 14.

Entry of the following amendments is respectfully requested.

In the Title

Amend the title to read as follows:

"Venlafaxine Extended Release Formulations"

In the Claims

Cancel claim 1.

Amend claims 2, 3, 5-8, and 15-18 as follows:

04/20/1999 SREBTA 0000076 011425 08964328
01 FC:102 78.00 25
02 FC:103 90.00 25
03 FC:117 870.00 25

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Patent

A1 2. (Amended) An extended release formulation [according to claim 1] of venlafaxine hydrochloride spheroids in a capsule wherein the spheroids are comprised of about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP. ~

3. (Amended) An [encapsulated,] extended release formulation of venlafaxine hydrochloride according to claim [1] 2 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

<u>Time (hours)</u>	<u>Average % Venlafaxine HCl released</u>
2	<30
4	30-55
8	55-80
12	65-90
24	>80. --

5. (Amended) [A composition] An extended release formulation according to claim 2 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight). ~

A2 6. (Amended) [A composition] An extended release formulation according to claim 2 wherein the film coating comprises 6- 8% by weight of total weight. ~

7. (Amended) [A composition] An extended release formulation according to claim 2 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight). ~

8. (Amended) [A composition] An extended release formulation according to claim 2 wherein film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%. ~

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A3 ~11. (Amended) An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 85% ethyl cellulose type HG 2834 and 15% hydroxypropyl-methylcellulose type 2910 sufficient to give coated spheroids having [a dissolution profile which gives the desired release rate over a 24 hour period] the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

<u>Time (hours)</u>	<u>Average % Venlafaxine HCl released</u>
2	<30
4	30-55
8	55-80
12	65-90
24	>80. ~

A4 ~ 15. (Amended) An extended release formulation [according to claim 1] of venlafaxine hydrochloride spheroids in a capsule wherein the spheroids are comprised of about 6% to 40% venlafaxine hydrochloride by weight, about 50% to about [940%] 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP. ~

~ 16. (Amended) An [encapsulated,] extended release formulation of venlafaxine hydrochloride according to claim 15 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

<u>Time (hours)</u>	<u>Average % Venlafaxine HCl released</u>
2	<30
4	30-55
8	55-80
12	65-90
24	>80. ~

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Patent

A4
Cont'd
~ 17. (Amended) An extended release formulation according to claim [14] 15 wherein the spheroids are composed of about 8.25% by weight of venlafaxine hydrochloride and about 91.75% by weight of microcrystalline cellulose, with a coating of from 3 to 5 % by weight of the total weight. ~

~ 18. (Amended) An extended release formulation according to claim [14] 15 wherein the spheroids are composed of about 16.5% by weight of venlafaxine hydrochloride and about 83.5% by weight of microcrystalline cellulose, with a coating of from 4 to 6 % by weight of the total weight. ~

Add new claims 19-26 as follows:

~ 19. An extended release formulation of venlafaxine hydrochloride spheroids in a capsule according to claim 15 wherein the capsule is a hard gelatin capsule. ~

~ 20. An extended release formulation of venlafaxine hydrochloride spheroids in a capsule according to claim 2 wherein the capsule is a hard gelatin capsule. ~

A5
~ 21. A method according to claim 13 wherein the extended release formulation is encapsulated in a hard gelatin capsule. ~

~ 22. A method according to claim 14 wherein the extended release formulation is encapsulated in a hard gelatin capsule. ~

~ 23. Coated spheroids of venlafaxine hydrochloride for extended release, said spheroids comprising venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose and being coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. ~

~ 24. An extended release dosage form of venlafaxine hydrochloride comprised of a capsule filled with a therapeutically effective amount of coated spheroids of venlafaxine chloride according to claim 23. ~

~ 25. An extended release dosage form of venlafaxine hydrochloride according to claim 24 wherein the capsule is made of hard gelatin. ~

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PatentA5
Cond

~26 An extended release formulation of venlafaxine hydrochloride according to claim 24 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

<u>Time (hours)</u>	<u>Average % Venlafaxine HCl released</u>
2	<30
4	30-55
8	55-80
12	65-90
24	>80. ~

Remarks

Entry of the amendments to the claims presented above is respectfully solicited.

Amendments to the Claims

By the foregoing amendment, Claim 2 is put in independent form and is therefore in condition for allowance. Claim 3 is amended to be dependent upon claim 2 rather than claim 1. Claims 5-8 are amended to be directed to "An extended release formulation" rather than a "composition" for proper dependency from claim 2. Claims 9 and 10 are already properly dependent from claim 2. Therefore, claims 3-10 are now all properly dependent upon allowable claim 2 and are also allowable.

Allowed Claim 11 is amended to include the disclosed dissolution profile.

By the foregoing amendment, Claim 15 is also put in independent form and the typographical error concerning the upper percentage of microcrystalline cellulose has been corrected. Therefore, claim 15 is in condition for allowance. Dependent Claim 16 is amended to remove the incorrect word "encapsulated". By the foregoing amendments, the dependency of claims 17 and 18 has been corrected from claim 14 to claim 15. Therefore, amended claims 16, 17 and 18 are also in condition for allowance.

New claims 19-22 are dependent upon allowable claims 15, 2, 13 and 14, respectively, and are directed to the hard gelatin capsule form. New claims 19-22 are therefore allowable also.

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Patent

Cancelled Claim 1 is replaced by Claim 23 which is directed to the gravamen of Applicants' invention, namely, the coated spheroids containing venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose for extended release. New Claims 24 and 25, dependent upon Claim 23 are directed to a dosage form in a capsule and in a hard gelatin capsule, respectively, containing the coated spheroids of Claim 23. New claim 26 is directed to the extended release dosage form of Claim 23 having the disclosed dissolution rate.

Rejection of Claim 1 (new Claim 23) for obviousness

The rejection of Claim 1 under 35 USC 103 for obviousness over McAnish et al. (US Patent 4,138,475) in view of Wong et al. (US 5,552,429) is respectfully traversed. (Claim 1 has been cancelled and replaced by new Claim 23.) McAnish is relied upon for showing a hard gelatin capsule comprised of spheroids containing an admixture of the active ingredient propranolol HCl and microcrystalline cellulose and coated with ethyl cellulose and hydroxypropylmethyl cellulose. As noted by the Examiner, venlafaxine is not mentioned in this disclosure. (Additionally, venlafaxine and propranolol are not structurally related.) Wong et al. is relied upon for teaching extended release dosage forms comprised of the same ingredients as McAnish et al. including the drugs venlafaxine and propranolol.

The Examiner's statement of the teaching of Wong et al. is incorrect. Wong et al. is not directed to providing sustained/extended release compositions and only discloses the existence of particular sustained release compositions for pindolol. Rather, Wong et al. discloses a method of potentiating the action of a first component chosen from flouxetine, venlafaxine, milnacipran, and duloxetine in increasing the availability of serotonin, norepinephrine and dopamine in the brain, comprising administering such first component in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and compounds of a given structural formula I. (See col. 1, line 65, through col. 2, line 10.) In fact, the dose of venlafaxine indicated in col. 6, lines 54-55, is from about 10 to about 150 mg once-thrice/day; preferred, from 25 to 125 mg thrice/day.

At page 7, lines 33-65, Wong et al. discusses the preference of combining the two components in one dosage form. However, they state that this may not be possible for the desired combination. At col. 8, lines 35-53, i.e. after the disclosure of

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Patent

referencing specific pindolol sustained release formulations, Wong et al. states that the second component may possibly be used in its sustained release formulation in its combination with the first component in order to provide substantially constant blood levels of the second component. Moreover, under "Benefits of the Invention", at col. 13, lines 32-44, Wong et al. states that the invention provides a more rapid onset of action than is usually provided by treatment of fluoxetine or duloxetine alone. Thus, it is clear that it is not an object of Wong et al. to provide new sustained release formulations of the first and second components alone or combined.

Finally, none of the 8 exemplified formulations includes venlafaxine. The two formulations including microcrystalline cellulose, that is, Formulations 4 and 5, include substantial portions of at least one other pharmaceutical excipient-but not hydroxypropylmethylcellulose.

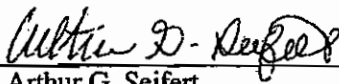
For these reasons, the teaching of Wong et al. is deemed not particularly relevant to Applicants' invention of coated spheroids of venlafaxine hydrochloride for extended release.

Further, the teaching of a sustained release formulation of microcrystalline cellulose and propranolol hydrochloride in McAnish et al. is not deemed sufficiently relevant to venlafaxine because the two compounds are not structurally related. Moreover, there is a tremendous difference in water solubility of the two compounds. The water solubility of propranolol hydrochloride is 93 mg/ml, whereas that of venlafaxine hydrochloride is 574 mg/ml - i.e. 6 fold greater. Therefore, Applicants' invention, as claimed in claims 23, 2 and 15, is indeed unobvious.

In view of the foregoing amendments and Remarks, Applicants respectfully solicit allowance of Claims 2-26, as amended or newly presented herein..

Respectfully submitted,

Date: April 13, 1999


Arthur G. Seifert
Reg. No. 28,040
Telephone (610) 902-2627


UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
 Washington, D.C. 20231

HL

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/964,328	11/05/97	SHERMAN	D AHP-95011-1-

 HM12/0721
 RONALD W ALICE
 AMERICAN HOME PRODUCTS CORPORATION
 PATENT LAW DEPARTMENT
 ONE CAMPUS DRIVE
 PARSIPPANY NJ 07054

EXAMINER

SPEAR, J

ART UNIT	PAPER NUMBER
1615	10

DATE MAILED: 07/21/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

WYETH 002-000741

Office Action SummaryApplication No.
08/964,328

Applicant(s)

SHERMAN, ET AL.

Examiner

JAMES M. SPEAR

Group Art Unit

1615

☒ Responsive to communication(s) filed on Apr 16, 1999☐ This action is **FINAL**.☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire THREE month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims☒ Claim(s) 2-26 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) 2-22 is/are allowed.☒ Claim(s) 23-26 is/are rejected.☐ Claim(s) _____ is/are objected to.☐ Claims _____ are subject to restriction or election requirement.**Application Papers**☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.☐ The drawing(s) filed on _____ is/are objected to by the Examiner.☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.☐ The specification is objected to by the Examiner.☐ The oath or declaration is objected to by the Examiner.**Priority under 35 U.S.C. § 119**☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).**Attachment(s)**☐ Notice of References Cited, PTO-892☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____☐ Interview Summary, PTO-413☐ Notice of Draftsperson's Patent Drawing Review, PTO-948☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Application/Control Number: 08/964,328

Page 2

Art Unit: 1615

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over McAinsh et al. U.S. 4,138,475 in view of Wong et al. U.S. 5,552,429.

The claims are rejected for the reasons set forth in Paper No. 7 as applied to now canceled claim 1. Applicants' arguments filed April 16, 1999 have been fully considered but they are not persuasive. Applicants state that, as noted by the examiner, venlafaxine is not mentioned in the McAinsh et al. reference. Applicants further state that venlafaxine and propranolol are not structurally related. This is true, however the only difference in the McAinsh et al. reference is that the only drug disclosed is propranolol. Wong et al. is not relied on for showing a sustained release dosage form of either drug, but is relied on for teaching that it is known the two drugs can be combined and administered together. To one skilled in the art with the disclosure of both McAinsh et al. and Wong et al. displayed together it would be reasonable to expect possible combinations. It would have been obvious to one of ordinary skill in the art to use the Wong et al. venlafaxine in the McAinsh et al. sustained release dosage form comprised of spheroids. Propranolol common to both McAinsh et al. and Wong et al. can be combined with venlafaxine. A combination of both in a sustained release dosage form would increase patient compliance when the need arises to administer the two together. The scope of applicant's claims in reciting

WYETH 002-000743

Application/Control Number: 08/964,328

Page 3

Art Unit: 1615

comprising does not exclude additional active agents. A dosage form of propranolol alone or propranolol and venlafaxine meets the limitations of applicants' claims.

Claims 2-22 are allowed. Claim 1 has been canceled. Claims 23-26 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James M. Spear whose telephone number is (703) 308-2457. The examiner can normally be reached on Monday thru Friday from 6:30 A.M. to 3:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for this Group is (703) 305-3592 or 308-4556.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

WYETH 002-000744

Application/Control Number: 08/964,328

Page 4

Art Unit: 1615

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

James M. Spear

July 9, 1999

James M. Spear
PRIMARY EXAMINER
ART UNIT 1615

WYETH 002-000745

PAPER # 11 : MISSING
FROM THE FILE

WYETH 002-000746

I HEREBY CERTIFY THAT THIS CORRESPONDENCE
 DEPOSITED WITH THE U.S. PATENT & TRADEMARK OFFICE
 FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO:
 ASSISTANT COMMISSIONER FOR PATENTS,
 WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

DATE

1/20/00

AHP-95011 P2



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman et al.

Serial No.: 08/964,328

Examiner: J. Spear

Filed: November 5, 1997

Art Unit: 1615

For: Extended Release Formulation

Assistant Commissioner for Patents
 Washington, D.C. 20231

PETITION AND FEE FOR EXTENSION OF TIME [37 CFR 1.136 (a)]

Sir:

1. This is a petition for an extension of time to respond to the Official Action dated July 21, 1999. Applicants hereby request an extension of time for a period of 3 month(s), as specified below.

2. Applicants are other than a small entity.

3. <u>Extention (months)</u>	<u>Fee for other than a small entity</u>
() one month	\$110.00
() two months	\$380.00
(x) three months	\$870.00
() four months	\$1360.00

Fee Due: \$870.00

01/24/2000 SDJ/KMG 00000056 011425 08964328
 01 FC:117 870.00 CH

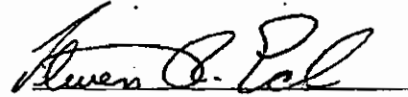
WYETH 002-000759

AHP-95011 P2

This application will be abandoned in favor of a continuation-in-part application which is being filed on January 20, 2000.

4. The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required by this paper to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this Petition are enclosed.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Steven R. Eck", is written over a horizontal line.

Steven R. Eck
Reg. No. 36,126

Dated: January 19, 2000

Telephone: (610) 902-2628

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING
DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS
FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO:
ASSISTANT COMMISSIONER FOR PATENTS,
WASHINGTON, DC, 20231 ON THE DATE APPEARING BELOW.

01-21-00

Gp 1615

AHP-95011 P2

DATE

1/26/00



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman et al.

Serial No.: 08/964,328

Examiner: J. Spear

Filed: November 5, 1997

Art Unit: 1615

For: Extended Release Formulation

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JAN 31 2000

Assistant Commissioner for Patents
Washington, D.C. 20231

PETITION AND FEE FOR EXTENSION OF TIME [37 CFR 1.136 (a)]

Sir:

1. This is a petition for an extension of time to respond to the Official Action dated July 21, 1999. Applicants hereby request an extension of time for a period of 3 month(s), as specified below.

2. Applicants are other than a small entity.

3. <u>Extention (months)</u>	<u>Fee for other than a small entity</u>
() one month	\$110.00
() two months	\$380.00
(x) three months	\$870.00
() four months	\$1360.00

Fee Due: \$870.00

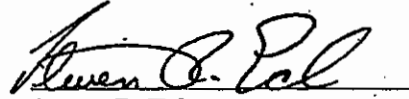
WYETH 002-000761

AHP-95011 P2

This application will be abandoned in favor of a continuation-in-part application which is being filed on January 20, 2000.

4. The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required by this paper to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this Petition are enclosed.

Respectfully submitted,

A handwritten signature in dark ink, appearing to read "Steven R. Eck", is written over a horizontal line.

Steven R. Eck
Reg. No. 36,126

Dated: January 19, 2000

Telephone: (610) 902-2628


**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/964,328	11/05/97	SHERMAN	D AHP-95011-1-
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EXAMINER

HM12/0216

RONALD W ALICE
AMERICAN HOME PRODUCTS CORPORATION
PATENT LAW DEPARTMENT
ONE CAMPUS DRIVE
PARSIPPANY NJ 07054

SPEAR, J

ART UNIT

PAPER NUMBER

1615

DATE MAILED:

02/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

WYETH 002-000763

Notice of AbandonmentApplication No.
08/964,328

Applicant(s)

SHERMAN, ET AL.

Examiner

JAMES M. SPEAR

Group Art Unit

1615

This application is abandoned in view of:

☒ applicant's failure to timely file a proper response to the Office letter mailed on Jul 21, 1999.☐ A response (with a Certificate of Mailing or Transmission of _____) was received on _____, which is after the expiration of the period for response (including a total extension of time of _____ month(s)) which expired on _____.☐ A proposed response was received on _____, but it does not constitute a proper response to the final rejection.

(A proper response to a final rejection consists only of: a timely filed amendment which places the application in condition for allowance; a Notice of Appeal; or the filing of a continuing application under 37 CFR 1.62 (FWC)).

☒ No response has been received.☐ applicant's failure to timely pay the required issue fee within the statutory period of three months from the mailing date of the Notice of Allowance.☐ The issue fee (with a Certificate of Mailing or Transmission of _____) was received on _____.☐ The submitted issue fee of \$ _____ is insufficient. The issue fee required by 37 CFR 1.18 is \$ _____.☐ The issue fee has not been received.☐ applicant's failure to timely file new formal drawings as required in the Notice of Allowability.☐ Proposed new formal drawings (with a Certificate of Mailing or Transmission of _____) were received on _____.☐ The proposed new formal drawings filed _____ are not acceptable.☐ No proposed new formal drawings have been received.☐ the express abandonment under 37 CFR 1.62(g) in favor of the FWC application filed on _____.☐ the letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.☐ the letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.☐ the decision by the Board of Patent Appeals and Interferences rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.☐ the reason(s) below:

James M. Spear
 PRIMARY EXAMINER
 ART UNIT 1615

PTO/SSB (11-98)

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Patent and Trademark Office U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)

RECEIVED

SEP 25 2001

File Information Unit

In re Application of

Sherman et al.

Application Number

08/964,328

Filed

11/05/97

Group Art Unit

Examiner

1615

Spear, 14

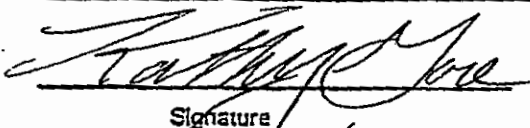
Paper No.

Assistant Commissioner for Patents
Washington, DC 20231

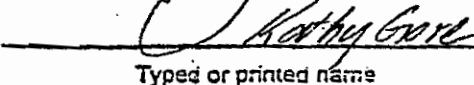
I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE)

☒ (A) referred to in United States Patent Number 6274171 column 1☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____ filed _____ on page _____ of paper number _____☐ (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____ filed _____ or☐ (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:



Signature

9/25/01
Date

Typed or printed name

FOR PTO USE ONLY

Approved by: _____

(initials)

Unit: _____

This form is estimated to take 0.2 hours to complete. It may vary depending upon the needs of the individual. It should be sent to the Chief Information Officer, Patent and Trademark Office, U.S. Department of Commerce, Room 3000, 14th Street, NW, Washington, DC 20540. SEND TO:

WYETH 002-000765

Approved
Patent and Trademark Ct.PTO/BB/68 (11-96)
through 10/31/99, OMB 0831-0031
U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)

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File Information Unit

In re Application of

Application Number

Filed

08/964328

11-05-97

Group Art Unit

Examiner

Paper No. #15

Assistant Commissioner for Patents
Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE)

☒ (A) referred to in United States Patent Number 6274171, column _____

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____, filed _____, on page _____ of paper number _____.

☐ (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____, or

☐ (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

Shawib Uppor

Signature

01-24-02

Date

Shawib Uppor

Typed or printed name

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Approved by:

(Initials)

Unit:

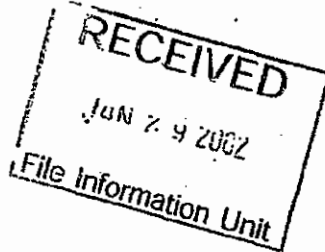
JAN 24 2002

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Assistant Commissioner for Patents, Washington, DC 20231.

WYETH 002-000766

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REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)



In re Application of	
Application Number	Filed
08/964,328	11/5/97
Group Art Unit	Examiner
12/15	Spec

Paper No. 16

Assistant Commissioner for Patents
 Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE)

- ___ (A) referred to in United States Patent Number 6,274,171 column ___
- ___ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____, filed _____, on page _____ of paper number _____.
- ___ (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____, or
- ___ (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

Specialized Patent Services 1/29/02
 Signature Date

Typed or printed name

FOR PTO USE ONLY

Approved by: _____
 (Initials)

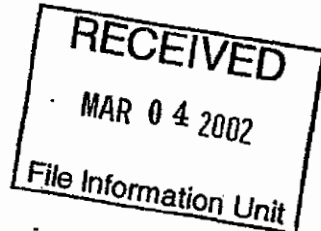
Unit: _____

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WYETH 002-000767

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REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(e)



In re Application of

Application Number

Filed

Group Art Unit

Examiner

08-964328 Nov 5, 1997

Paper No. #17

Assistant Commissioner for Patents
Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE)

- ___ (A) referred to in United States Patent Number 6274171 column ___
- ___ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____, filed _____, on page _____ of paper number _____
- ___ (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____
- ___ (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

Darlene Jones

Signature

3/4 - 02

Date

Darlene Jones

Typed or printed name

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Approved by:

(Initials)

Unit:

Bureau Hour Statement: This form is estimated to take 6.2 hours to complete. It will vary depending upon the needs of the case. Any comments on the amount of time you are requested to contribute should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEE OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Patent and Trademark Office, Washington, DC 20231.

WYETH 002-000768

PTO/SB/66 (04-01)

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)							
<div style="border: 1px solid black; padding: 5px; width: fit-content; margin-bottom: 20px;"> REC-100 MAR 8 2002 File Information Unit </div> <p>Assistant Commissioner for Patents Washington, DC 20231</p>	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td colspan="2" style="padding: 5px;">In re Application of</td> </tr> <tr> <td style="width: 60%; padding: 5px;">Application Number 08/964328</td> <td style="width: 40%; padding: 5px;">Filed</td> </tr> <tr> <td style="padding: 5px;">Art Unit</td> <td style="padding: 5px;">Examiner</td> </tr> </table> <p style="text-align: right; margin-top: 20px;">Paper No. 15</p>	In re Application of		Application Number 08/964328	Filed	Art Unit	Examiner
In re Application of							
Application Number 08/964328	Filed						
Art Unit	Examiner						
<p>1. <input type="checkbox"/> I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)</p> <p><input type="checkbox"/> (A) referred to in:</p> <p>United States Patent Application Publication No. 08/964328, page _____, line _____, United States Patent Number 627471, column _____, line _____, or an International Application which was filed on or after November 29, 2000 and which designates the United States, WIPO Pub. No. _____, page _____, line _____.</p> <p><input type="checkbox"/> (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or 1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.</p> <p>2. <input type="checkbox"/> I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.</p> <div style="display: flex; justify-content: space-between; margin-top: 30px;"> <div style="width: 45%;"> <p style="font-size: 1.2em; margin-bottom: 5px;"><i>Mo Johnson</i></p> <p style="text-align: center; margin-bottom: 10px;">Signature</p> <p style="font-size: 1.2em; margin-bottom: 5px;">MOE JOHNSON</p> <p style="text-align: center; margin-bottom: 10px;">Typed or printed name</p> </div> <div style="width: 45%; text-align: center;"> <p style="font-size: 1.5em; margin-bottom: 5px;">3802</p> <p style="margin-bottom: 10px;">Date</p> </div> </div> <div style="border: 1px solid black; padding: 5px; width: fit-content; margin-top: 10px; float: right;"> <p style="text-align: center; margin: 0;">FOR PTO USE ONLY</p> <p>Approved by: <i>[Signature]</i></p> <p style="text-align: center; font-size: 0.8em;">(initials)</p> <p>Unit: _____</p> </div>							

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

WYETH 002-000769

PTO/SB/58 (04-01)

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

In re Application of

Application Number

06/969328

Filed

11-5-97

Art Unit

Examiner

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JUN 19 2002

File Information Unit

Paper No. #19

Assistant Commissioner for Patents
Washington, DC 20231

1. ☒ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☒ (A) referred to in:

United States Patent Application Publication No. 6279171, page _____, line _____,

United States Patent Number _____, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.


2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.



Signature

6-19-02

Date



Typed or printed name

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Approved by: Unit: 

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

WYETH 002-000770

PTO/S3/63 (04-01)

Approved for use through 10/31/2002. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

RECEIVED
JUL 23 2002
File Information Unit

In re Application of

Application Number

Filed

Art Unit

Examiner

Paper No. #20

Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:

United States Patent Application Publication No. 6403120, page _____, line _____,

United States Patent Number _____, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

David E. Less
Signature

7/23/02
Date

DAVID E. LESS
Typed or printed name

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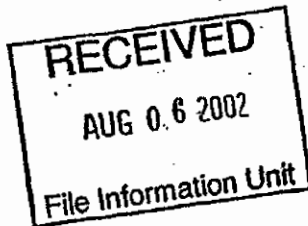
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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)



In re Application of

Application Number

08-964328

Filed

11-5-97

Art Unit

Examiner

Paper No. #21

Assistant Commissioner for Patents
 Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:

United States Patent Application Publication No. _____, page _____, line _____

United States Patent Number 6403120, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Telleria

Signature

8-6-02

Date

Victor Telleria

Typed or printed name

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(initials)

Unit: _____

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PTO/SB/52 (04-01)

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

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File Information Unit

In re Application of

Application Number

08-964328

Filed

11-5-97

Art Unit

Examiner

Paper No. #22

Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

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United States Patent Application Publication No. _____, page _____, line _____,

United States Patent Number 6274171, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Moe Johnson
Signature

9 18 02

Date

MOE JOHNSON
Typed or printed name

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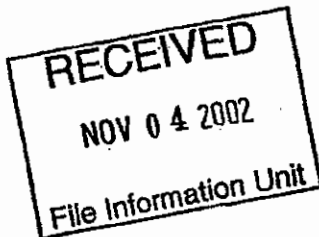
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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)



In re Application of

Application Number

08/964 328

Filed

Nov 5, 1997

Art Unit

1615

Examiner

Spear

Paper No. 23

Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:United States Patent Application Publication No. 6419958, page _____, line _____,

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1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Darlene Jones

Signature

Date

Darlene Jones

Typed or printed name

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REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(A)

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In re Application of **Sherman, et al.**

Application Number 08/964,328

Filed 11/5/97

Group Art Unit

Examiner

Paper No.

Assistant Commissioner for Patients
Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above identified ABANDONED application, which is: (CHECK ONE)

- ☒ (A) referred to in United States Patent Number 6,274,171, column ____.
- ☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____, filed _____, on page _____ of paper number _____.
- ☐ (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____, or
- ☐ (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

Cantwell and Paxton, Inc.

Signature

Type or Printed Name

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)**RECEIVED****FEB 11 2003**

File Information Unit

In re Application of

Application Number

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Art Unit

Examiner

Paper No. #25Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:United States Patent Application Publication No. 6274171, page _____, line _____,

United States Patent Number _____, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

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☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

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2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Anda Nyles
SignatureAnda Nyles
Typed or printed name

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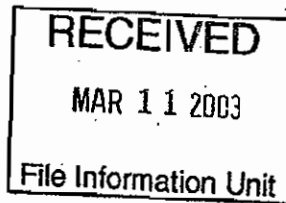
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PTO/S2/85 (04-01)

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)



In re Application of <u>Sherman</u>	
Application Number <u>08964328</u>	Filed <u>11/5/97</u>
Art Unit	Examiner

Paper No. 216Assistant Commissioner for Patents
Washington, DC 20231

1. ☐ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:United States Patent Application Publication No. 6274171, page _____, line _____.

United States Patent Number _____, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Signature

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Unit: <u>File Information Unit</u>

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WYETH 002-000777

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

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APR 24 2003
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In re Application of <u>Sherman</u>	
Application Number <u>08/964328</u>	Filed <u>11/5/97</u>
Art Unit	Examiner

Paper No. #27

Assistant Commissioner for Patents
Washington, DC 20231

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☐ (A) referred to in:

United States Patent Application Publication No. 6274171, page _____, line _____,

United States Patent Number _____, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Anita Myles
Signature
Anita Myles
Typed or printed name

4/24/03
Date

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WYETH 002-000778



US006274171B1

(12) **United States Patent**
Sherman et al.

(10) Patent No.: **US 6,274,171 B1**

(45) Date of Patent: **Aug. 14, 2001**

(54) **EXTENDED RELEASE FORMULATION OF
 VENLAFAXINE HYDROCHLORIDE**

(75) Inventors: Deborah M. Sherman, Plattsburgh;
 John C. Clark, Peru, both of NY (US);
 John U. Lamer, St. Albans, VT (US);
 Steven A. White, Champlain, NY (US)

(73) Assignee: American Home Products
 Corporation, Madison, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this
 patent is extended or adjusted under 35
 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 09/488,629

(22) Filed: Jan. 20, 2000

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/964,328, filed on
 Nov. 5, 1997, now abandoned, which is a continuation-in-
 part of application No. 08/821,137, filed on Mar. 20, 1997,
 now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25,
 1996.

(51) Int. Cl.⁷ A61K 9/52; A61K 9/54;
 A61K 9/62

(52) U.S. Cl. 424/461; 424/457; 424/458;
 424/459; 514/781; 514/962

(58) Field of Search 424/495, 494,
 424/461, 458, 459, 457, 456, 462

(56) **References Cited**

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* cited by examiner

Primary Examiner—James M. Spear

(74) Attorney, Agent, or Firm—Rebecca R. Barrett

(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage
 formulation and unit dosage form thereof of venlafaxine
 hydrochloride, an antidepressant, which provides better con-
 trol of blood plasma levels than conventional tablet formu-
 lations which must be administered two or more times a day
 and further provides a lower incidence of nausea and vom-
 iting than the conventional tablets. More particularly, the
 invention comprises an extended release formulation of
 venlafaxine hydrochloride comprising a therapeutically
 effective amount of venlafaxine hydrochloride in spheroids
 comprised of venlafaxine hydrochloride, microcrystalline
 cellulose and, optionally, hydroxypropylmethylcellulose
 coated with a mixture of ethyl cellulose and hydroxypropy-
 lmethylcellulose.

25 Claims, No Drawings

WYETH 002-000779

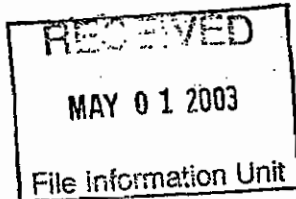
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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)



In re Application of

Sherman et al

Application Number

08/964,328

Filed

11/5/97

Art Unit

Examiner

Paper No. *#28*Assistant Commissioner for Patents
Washington, DC 20231

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☐ (A) referred to in:

United States Patent Application Publication No. _____, page _____, line _____.

United States Patent Number *6274071*, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which

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☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or

1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☐ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Signature

4/29/03
Date

Nancy P. [illegible]
Typed or printed name

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										1ST EXAMINER		DATE			
										2ND EXAMINER		DATE			
68534 U.S. PTO 08/96328  11/05/97		APPLICATION NUMBER		TYPE APPL		FILING DATE		SPECIAL HANDLING		GROUP ART UNIT		CLASS		SHEETS OF DRAWING	
						MONTH DAY YEAR									
TOTAL CLAIMS		INDEPENDENT CLAIMS		SMALL ENTITY?		FILING FEE		FOREIGN LICENSE		ATTORNEY DOCKET NUMBER					
CONTINUITY DATA															
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PCT/FOREIGN APPLICATION DATA															
FOREIGN PRIORITY CLAIMED		COUNTRY CODE		PCT/FOREIGN APPLICATION SERIAL NUMBER		PCT/FOREIGN APPLICATION SERIAL NUMBER		FOREIGN FILING DATE							

WYETH 002-000781

TITLE OF INVENTION <div style="border: 1px solid black; height: 150px; width: 100%;"></div>		ATTORNEY REGISTRATION NUMBERS <div style="border: 1px solid black; height: 150px; width: 100%;"></div>		CORRESPONDENCE NAME AND ADDRESS <div style="border: 1px solid black; height: 150px; width: 100%;"></div>		APPLICANT/INVENTOR DATA <div style="border: 1px solid black; height: 150px; width: 100%;"></div>	
AUTHORITY CODE		FAMILY NAME		NAME SUFFIX		STATE/COUNTRY CODE	
		GIVEN NAME					
		TY					
AUTHORITY CODE		FAMILY NAME		NAME SUFFIX		STATE/COUNTRY CODE	
		GIVEN NAME					
		TY					
							MORE <input type="checkbox"/>

U.S. Government Printing Office: 1996 - 004-474/0903

WYETH 002-000782

1-11-13-14- PATENT APPLICATION FEE DETERMINATION RECORD Effective October 1, 1997					Application or Docket Number	
CLAIMS AS FILED - PART I (Column 1) (Column 2)						
FOR	NUMBER FILED	NUMBER EXTRA				
BASIC FEE						
TOTAL CLAIMS	18	minus 20 = *				
INDEPENDENT CLAIMS	4	minus 3 = * 1				
MULTIPLE DEPENDENT CLAIM PRESENT						
* If the difference in column 1 is less than zero, enter "0" in column 2						
CLAIMS AS AMENDED - PART II (Column 1) (Column 2) (Column 3)						
AMENDMENT A						
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		
	Total	25	Minus	** 20	= 5	
	Independent	4	Minus	*** 5	= 1	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					
AMENDMENT B						
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		
	Total	*	Minus	**	=	
	Independent	*	Minus	***	=	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					
AMENDMENT C						
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		
	Total	*	Minus	**	=	
	Independent	*	Minus	***	=	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20." *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3." The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.						

SMALL ENTITY TYPE <input type="checkbox"/>		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
	395.00	OR		790.00
x\$11=		OR	x\$22=	
x41=		OR	x82=	82
+135=		OR	+270=	
TOTAL		OR	TOTAL	872

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
x\$11=		OR	x\$22=	980
x41=		OR	x82=	780
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

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(FILE 'USPAT' ENTERED AT 16:51:39 ON 27 SEP 1998)

L1	21 S VENLAFAXINE?
L2	19 S L1 AND CAPSULE?
L3	0 S L2 AND CAPSULE?/CLM
L4	2 S VENLAFAXINE?(P)CAPSULE?
L5	0 S L4 AND MICROCRYSTALLINE?
L6	15 S VENLAFAXINE? AND MICROCRYSTALLINE?
L7	14 S L6 AND CAPSULE?
L8	12 S L7 AND COAT?
L9	12 S L8 AND ETHYLCELLULOSE?
L10	7 S L9 AND HYDROXYPROPYLMETHYL?

=> D L10 1-7

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5. 5,532,264, Jul. 2, 1996, Potentiation of drug response; David T. Wong, et al., 514/415, 211, 224.2, 230.5, 259, 312, 367, 373, 375, 394, 406, 418, 438, 443, 624, 652, 654 [IMAGE AVAILABLE]
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7. 5,532,244, Jul. 2, 1996, Potentiation of drug response; David T. Wong, et al., 514/255, 256, 438, 620, 654 [IMAGE AVAILABLE]

WYETH 002-000784

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POSITION	ID NO.	DATE
CLASSIFIER	32	1/24/98
EXAMINER	10322	2-20-98
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INDEX OF CLAIMS

Claim	Date
Final Original	9/28/98
1	✓
2	✓
3	✓
4	✓
5	✓
6	✓
7	✓
8	✓
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10	0
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SYMBOLS

✓ Rejected
 = Allowed
 - (Through numbers) Cancelled
 R Restricted
 N Non-attached
 A Interference
 O Objected

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SEARCHED			
Class	Sub.	Date	Exmr.
424	451	9-27-98	8 p.m.
	452	"	"
	456	"	"
	457	"	"
	458	"	"
	459	"	"
	461	"	"
Above To Date		7-5-99	8 p.m.

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INTERFERENCE SEARCHED			
Class	Sub.	Date	Exmr

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66534 U.S. PTO

08/964328

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PATENT APPLICATION



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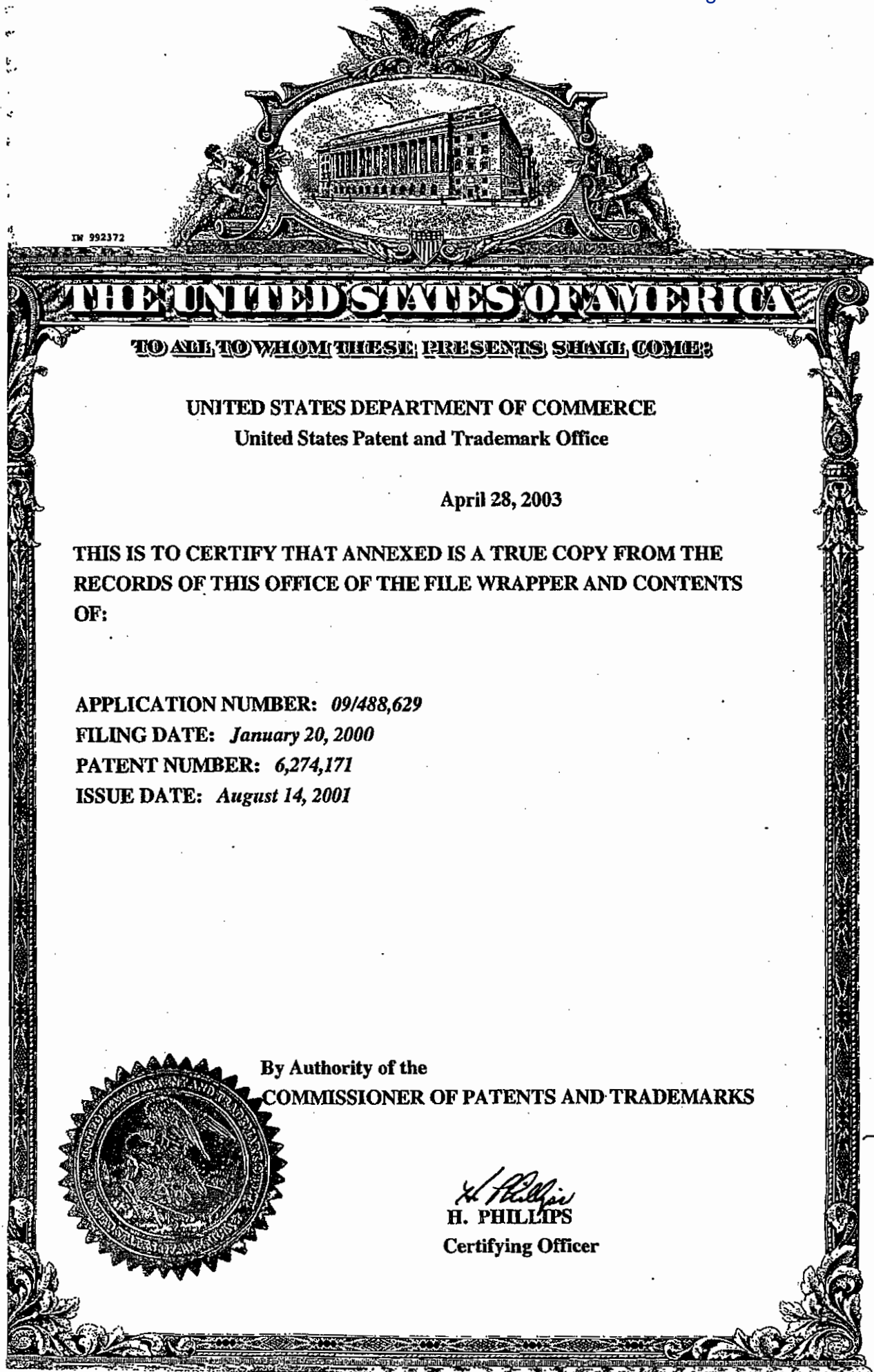
1.	Application papers.	
2.	Tr R2 Qd on 1200.	2-24-98
3.	LTR, RE, Bailin-Surcharge	3-26-98
4.	Disclosure Statement	2/13/98
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	14. Request for Appeal	9-25-01
	15. Request for Appeal	4/24/02
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EXHIBIT 13



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APPLICATION NUMBER: 09/488,629

FILING DATE: January 20, 2000

PATENT NUMBER: 6,274,171

ISSUE DATE: August 14, 2001



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

H. Phillips
H. PHILLIPS
Certifying Officer

WYETH 002-000001

3542 U.S. PTO
09/488629
01/20/00

424	461
Class	Subclass
ISSUE CLASSIFICATION	

PATENT NUMBER
6274171

U.S. UTILITY Patent Application

NO O.I.P.E. PATENT DATE
AUG 14 2007

APPLICANTS: Deborah Simon, John Clark, John Lamer

APPLICATION NO. 09/488629	CONT/PRIOR D.	CLASS 424	SUBCLASS 461	ART. UNIT 1615	EXAMINER SPEAR
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08/964,328

TITLE: Extended release formulation

PTO-2040
12/98

ISSUING CLASSIFICATION							
ORIGINAL		CROSS REFERENCE(S)					
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
424	461	424	457	458	459		
INTERNATIONAL CLASSIFICATION							
A61K	9/52	514	781	962			
A61K	9/54						
A61K	9/62						

☐ Continued on Issue Slip inside File Jacket

<input type="checkbox"/> TERMINAL DISCLAIMER	DRAWINGS			CLAIMS ALLOWED	
	Sheets Drwg. 0	Figs. Drwg. 0	Print Fig. 0	Total Claims 25	Print Claim for O.G. 1
<input type="checkbox"/> The term of this patent subsequent to _____ (date) has been disclaimed.	<p>JAMES M. SPEAR PRIMARY EXAMINER ART UNIT 1615 James M. Spear 5-7-01 (Date)</p>			NOTICE OF ALLOWANCE MAILED	
				5/09/01	
<input type="checkbox"/> The term of this patent shall not extend beyond the expiration date of U.S. Patent No. _____	<p>James M. Spear 5-7-01 (Date)</p>			ISSUE FEE	
				Amount Due 1240.00	Date Paid 6/18/01
<input type="checkbox"/> The terminal _____ months of this patent have been disclaimed.	<p>James M. Spear 5-7-01 (Date)</p>			ISSUE BATCH NUMBER G14	
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Bib Data Sheet

CONFIRMATION NO. 4728

SERIAL NUMBER 09/488,629	FILING DATE 01/20/2000 RULE	CLASS 424	GROUP ART UNIT 1615	ATTORNEY CLOCKET NO. AHP-95011-P2
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APPLICANTS

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John C. Clark, Peru, NY;
John U. Lamer, St. Albans, VT;
Steven A. White, Champlain, NY;

**** CONTINUING DATA *******

THIS APPLICATION IS A CIP OF 08/964,328 11/05/1997 ABN
WHICH IS A CIP OF 08/821,137 03/20/1997 ABN
AND CLAIMS BENEFIT OF 60/014,006 03/25/1996

**** FOREIGN APPLICATIONS *******

IF REQUIRED, FOREIGN FILING LICENSE
GRANTED ** 03/20/2000

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35 USC 119 (a-d) conditions met <input type="checkbox"/> yes <input checked="" type="checkbox"/> no <input type="checkbox"/> Met after Allowance				
Verified and Acknowledged Examiner's Signature <i>Shear</i> Initials				

ADDRESS

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TITLE

EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

FILING FEE RECEIVED 1228	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit
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US006274171B1

(12) **United States Patent**
Sherman et al.

(10) Patent No.: **US 6,274,171 B1**
 (45) Date of Patent: **Aug. 14, 2001**

(54) **EXTENDED RELEASE FORMULATION OF
 VENLAFAXINE HYDROCHLORIDE**

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 Corporation, Madison, NJ (US)

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(22) Filed: Jan. 20, 2000

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 now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25,
 1996.

(51) Int. Cl.⁷ A61K 9/52; A61K 9/54;
 A61K 9/62

(52) U.S. Cl. 424/461; 424/457; 424/458;
 424/459; 514/781; 514/962

(58) Field of Search 424/495, 494,
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4,138,475 * 2/1979 McAinsh et al. 424/19
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Primary Examiner—James M. Spear

(74) Attorney, Agent, or Firm—Rebecca R. Barrett

(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage
 formulation and unit dosage form thereof of venlafaxine
 hydrochloride, an antidepressant, which provides better control
 of blood plasma levels than conventional tablet formu-
 lations which must be administered two or more times a day
 and further provides a lower incidence of nausea and vom-
 iting than the conventional tablets. More particularly, the
 invention comprises an extended release formulation of
 venlafaxine-hydrochloride-comprising a therapeutically
 effective amount of venlafaxine hydrochloride in spheroids
 comprised of venlafaxine hydrochloride, microcrystalline
 cellulose and, optionally, hydroxypropylmethylcellulose
 coated with a mixture of ethyl cellulose and hydroxypropy-
 lmethylcellulose.

25 Claims, No Drawings

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EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

This application continuation-in-part of Application Ser. No. 08/964,328, filed Nov. 5, 1997 abandoned, which is a continuation-in-part of Application Ser. No. 08/821,137, filed Mar. 20, 1997 abandoned, which, in turn, claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose, with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl-cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid

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increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine is hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally,

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hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride is polymorphic. Of the forms

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isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19-24% and a hydroxypropoxy content of 4-13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a methoxy content of 44.0-51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2-5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50-55° C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70% dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

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Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

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EXAMPLE NO. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1-4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%, w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior to the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates	
Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable

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capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(SV)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.888 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule			
Time (hours)	75 mg (IR) tablet (q 12 h)	2 x 75 mg (ER) capsules (q 24 hr)	1 x 150 mg (ER) capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		

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TABLE 2-continued

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule			
Time (hours)	75 mg (IR) tablet (q 12 h)	2 x 75 mg (ER) capsules (q 24 hr)	1 x 150 mg (ER) capsules (q 24 h)
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hours intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/mL, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/mL, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg, conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level			
Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As

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quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20°C . until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 μL of a stock internal standard solution (150 $\mu\text{g}/\text{mL}$). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cmx4.6 mm, 5 μm ; column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model

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FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Ky. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/spherulization machine (Aeromatic-Fieldier Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns

Time/hr	% Dissolved 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

EXAMPLE NO. 7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing spheroids comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose; USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

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2. An extended release formulation of venlafaxine hydrochloride according to claim 1 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

3. An extended release formulation according to claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

4. An extended release formulation according to claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. An extended release formulation according to claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1% to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

7. An extended release formulation according to claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. An extended release formulation according to claim 1 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

9. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

10. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80

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-continued

Time (hours)	Average % Venlafaxine HCl released
12	65-90
24	>80

12. An extended release formulation according to claim 1 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose, and about 62% by weight of microcrystalline cellulose.

13. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

14. An extended release formulation according to claim 1 wherein the film coating comprises 6-8% by weight of total weight.

15. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

16. An extended release formulation according to claim 1 wherein the film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

17. An extended release formulation according to claim 1 wherein the film coating composition is comprised of about 85% by total weight of film coating of ethyl cellulose having 44.0-51% content of ethoxy groups and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

18. An extended release formulation according to claim 1 wherein the film coating composition is comprised of 85% by weight of ethyl cellulose having an ethoxy content of 44.0-51% and a viscosity of 50 cps for a 5% aqueous solution, and 15% by weight of hydroxypropylmethylcellulose having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12%.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose coated with a quantity of a mixture comprised of 85% ethyl cellulose and 15% hydroxypropylmethylcellulose sufficient to give coated spheroids having a dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C:

Time	Average % Venlafaxine HCl Released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides

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a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

21. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

23. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof,

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an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

24. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

25. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

* * * * *

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Washington, D.C. 20231Case Docket No. AHP-95011-P2
PATENT

Sir:

Transmitted herewith for filing is the patent application of

Inventor: Deborah M. Sherman et al.

For: Extended Release Formulation

This application is a:

- ☐ New Application ☒ CIP Application
- ☐ Divisional Application ☐ Continuation Application
of prior application No. 08/964,328. The entire disclosure of the prior
application, from which a copy of the oath or declaration is supplied, is
considered as being part of the disclosure of the accompanying application
and is hereby incorporated by reference.

Enclosed are:

0 sheets of drawing.

- ☐ Information Disclosure Statement.
- ☐ Preliminary Amendment.
- ☐ Signed statement attached deleting inventor(s) named in the prior application.

CLAIMS AS FILED				
(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) BASIC FEE \$690.00
TOTAL CLAIMS	22 -20 =	2	X 18.00	36.00
INDEPENDENT CLAIMS	6 -3 =	3	X 78.00	234.00
MULTIPLE DEPENDENT CLAIMS	0	0	250.00	0.00
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EXTENDED RELEASE FORMULATION

This application continuation-in-part of Application Serial No. 08/964,328, filed November 5, 1997, ^{ABANDONED} which is a continuation-in-part of copending Application No. 08/821,137, filed March 20, 1997, ^{ABANDONED} which, in turn, claims priority from Provisional Application No. 60/014,006 filed March 25, 1996.

Background of the Invention

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in US patent 4,966,768. US patent 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to

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form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. US patent 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propranolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in US patent 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

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Brief Description of the Invention

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a
5 twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time
10 profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine
15 hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In
20 contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in
25 need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that
30 attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was

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greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of

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total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

5 Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70 % to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of
10 hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

15 Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to
20 about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount
25 of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

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Detailed Description of the Invention

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19-24% and a hydroxypropoxy content of 4-13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis.

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Preferably the ethyl cellulose has a ethoxy content of 44.0-51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12%. The ethyl cellulose used herein is Aqualon
5 HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without
10 changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2-5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the
15 hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50-55°C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine
20 proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70%
25 dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone,
30 methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which

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could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

5

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

10

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

15

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

20

Example No. 1.

Venlafaxine Hydrochloride Extended Release Capsules

25

A mixture of 44.8 parts (88.4 % free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

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Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

5 To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

10 The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

Example No. 2

15 Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

Example No. 3

20 Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

Example No. 4

25 Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

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In the foregoing failed experiments and in Examples 1-4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an
5 hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this
10 invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

15 Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5 % (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

20 Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6 % (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2
25 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified
30 water at 37°C.

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Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

10

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Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules

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are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

5 The percentage of venlafaxine released is determined from the equation

10
$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

15 Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride
20 according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

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Table 2
Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended
release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 x 75 mg (ER)capsules (q 24 hr)	1 x 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

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Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

Table 3.

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20°C until analysis could be completed.

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To 1 mL of each plasma sample in a plastic tube was added 150 μ L of a stock internal standard solution (150 μ g/mL). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μ L portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μ L samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm x 4.6 mm, 5 μ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

Example No. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in

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combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

Example No. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Kentucky 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/speronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Maryland 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

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<u>Ingredient</u>	<u>% (w/w)</u>
T0180 Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following

5 dissolution patterns:

<u>Time/hr</u>	<u>% Dissolved</u> <u>16.5% / 5%</u>	<u>% Dissolved</u> <u>16.5% / 7%</u>
T0181 2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

Example No. 7

10 A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcrystalline cellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

<u>Time/hr</u>	<u>% Dissolved</u> <u>8.25% / 5%</u>
T0182 2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

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Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

Year	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	

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What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation according to Claim 1 wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

3. An extended release formulation according to Claim 2 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

4. An extended release formulation according to Claim 3 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to Claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

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a 6. An extended release formulation according to Claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1 % to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose,

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7. An extended release formulation according to Claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

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a 8. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose

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9. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

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10. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

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a 11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to Claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

30

Time (hours)

Average % Venlafaxine HCl released

2
4<30
30-55

T 6710

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WYETH 002-000033

20 January 2000

SRE/rk/apr

AHP-95011-P2

PATENT

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5 12. An extended release formulation according to claim 2 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62% by weight of microcrystalline cellulose.

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a 10 13. *An extended release formulation*
~~A composition~~ according to claim 2 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

a 15 14. *An extended release formulation*
~~A composition~~ according to claim 2 wherein the film coating comprises 6-8% by weight of total weight.

a 15 15. *An extended release formulation*
~~A composition~~ according to claim 2 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

20 16. *An extended release formulation*
~~A composition~~ according to claim 2 wherein ^{the} film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

25 17. *Sub 0.3*
A film coating composition according to Claim 2 which is comprised of about 85% by total weight of film coating of ethyl cellulose having a 44.0-51.0% content of ethoxy groups, and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

20 January 2000
SRE/rlk/apr
AHP-95011-P2
PATENT

-22-

18. A film coating composition according to Claim 2 which is comprised of 85% by weight of ethyl cellulose type HG 2834 and 15% by weight of hydroxypropylmethylcellulose type 2910.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 85% ethyl cellulose type HG 2834 and 15% hydroxypropylmethylcellulose type 2910 sufficient to give coated spheroids having a dissolution profile which gives the desired release rate over a 24 hour period.

20. An extended release formulation of venlafaxine hydrochloride according to Claim 2 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

21. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

09/488,629

ABSTRACT OF THE DISCLOSURE

5 This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride
10 comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

AHP-95011 P2
PATENT**DECLARATION AND POWER OF ATTORNEY**

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled Extended Release Formulation

, the specification of which

(check one) X is attached hereto.

_____ was filed on _____ as

Application Serial No. _____

and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Priority Claimed

Yes

No

(Number)

(Country)

(Day/Month/Year Filed)

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States Provisional Application(s) for Patent listed below:

60/014,006

(Provisional Appln. No.)

March 25, 1996

(Filing Date)

(Provisional Appln. No.)

(Filing Date)

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

WYETH 002-000037

AHP-95011 P2
PATENT

<u>08/821,137</u> (Application Serial No.)	<u>March 20, 1997</u> (Filing Date)	<u>Abandoned</u> (Status - Patented, pending, abandoned)
<u>08/964,328</u> (Application Serial No.)	<u>November 5, 1997</u> (Filing Date)	<u>Pending</u> (Status - Patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Egon E. Berg, Reg. No. 21,117, of One Campus Drive, Parsippany, New Jersey, 07054; and Rebecca R. Barrett, Reg. No. 35,152; Steven R. Eck, Reg. No. 36,126; Arnold S. Milowsky, Reg. No. 35,288; Michael R. Nagy, Reg. No. 33,432; George Tarnowski, Reg. No. 27,472; all of P.O. Box 8299, Philadelphia, Pennsylvania, 19101; and Daniel B. Moran, Reg. No. 41,204 of 401 N. Middletown Road, Pearl River, New York, 10965.

Address all telephone calls to Steven R. Eck at telephone number (610) 902-2628.

Address all correspondence to Egon E. Berg, American Home Products Corporation, Patent Law Department - 2B, One Campus Drive, Parsippany, New Jersey, 07054.

Full name of sole or first inventor Deborah M. Sherman

Inventor's signature _____ Date _____

Residence 5 Belmont Avenue, Plattsburgh, New York, 12901

Citizenship United States of America

Post Office Address Same as residence

Full name of second joint inventor, if any John C. Clark

Inventor's signature _____ Date _____

Residence 1 Rounds Drive, Peru, New York, 12972

Citizenship United States of America

Post Office Address Same as residence

Date _____

Post Office Address Same as residence

0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	0051	0052	0053	0054	0055	0056	0057	0058	0059	0060	0061	0062	0063	0064	0065	0066	0067	0068	0069	0070	0071	0072	0073	0074	0075	0076	0077	0078	0079	0080	0081	0082	0083	0084	0085	0086	0087	0088	0089	0090	0091	0092	0093	0094	0095	0096	0097	0098	0099	0100	0101	0102	0103	0104	0105	0106	0107	0108	0109	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125	0126	0127	0128	0129	0130	0131	0132	0133	0134	0135	0136	0137	0138	0139	0140	0141	0142	0143	0144	0145	0146	0147	0148	0149	0150	0151	0152	0153	0154	0155	0156	0157	0158	0159	0160	0161	0162	0163	0164	0165	0166	0167	0168	0169	0170	0171	0172	0173	0174	0175	0176	0177	0178	0179	0180	0181	0182	0183	0184	0185	0186	0187	0188	0189	0190	0191	0192	0193	0194	0195	0196	0197	0198	0199	0200	0201	0202	0203	0204	0205	0206	0207	0208	0209	0210	0211	0212	0213	0214	0215	0216	0217	0218	0219	0220	0221	0222	0223	0224	0225	0226	0227	0228	0229	0230	0231	0232	0233	0234	0235	0236	0237	0238	0239	0240	0241	0242	0243	0244	0245	0246	0247	0248	0249	0250	0251	0252	0253	0254	0255	0256	0257	0258	0259	0260	0261	0262	0263	0264	0265	0266	0267	0268	0269	0270	0271	0272	0273	0274	0275	0276	0277	0278	0279	0280	0281	0282	0283	0284	0285	0286	0287	0288	0289	0290	0291	0292	0293	0294	0295	0296	0297	0298	0299	0300	0301	0302	0303	0304	0305	0306	0307	0308	0309	0310	0311	0312	0313	0314	0315	0316	0317	0318	0319	0320	0321	0322	0323	0324	0325	0326	0327	0328	0329	0330	0331	0332	0333	0334	0335	0336	0337	0338	0339	0340	0341	0342	0343	0344	0345	0346	0347	0348	0349	0350	0351	0352	0353	0354	0355	0356	0357	0358	0359	0360	0361	0362	0363	0364	0365	0366	0367	0368	0369	0370	0371	0372	0373	0374	0375	0376	0377	0378	0379	0380	0381	0382	0383	0384	0385	0386	0387	0388	0389	0390	0391	0392	0393	0394	0395	0396	0397	0398	0399	0400	0401	0402	0403	0404	0405	0406	0407	0408	0409</
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I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING
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WASHINGTON, DC 20231, ON THE DATE APPEARING BELOW.

GA 11615

AHP-95011-1-C1
PATENT

TC 1600 MAIL ROOM

JUL 21 1999

RECEIVED

7/21/99

DATE

Robert J. Kelly
July 13, 1999



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman et al.

Serial No.: 08/964,328

Examiner: J. Spear

Filed: November 5, 1997

Group: 1615

For: Extended Release Formulation

Assistant Commissioner of Patents
Washington, DC 20231

SUPPLEMENTARY INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR 1.97(c)

Sir:

With respect to the subject matter of the above-identified application, the applicants have become aware of the following references, which may have relevance to the examination of the invention claimed.

WO 97/37640, published October 16, 1997; and
EP 0 797 991, published October 1, 1997

Form PTO-1449 and copies of the above references are enclosed.

The undersigned hereby states that each item contained in this Supplemental Information Disclosure Statement was cited in the PCT Search Report, dated June 1, 199, in the counterpart PCT application. Since this Supplemental Information Disclosure Statement is being submitted with three months of the PCT Search Report, no fee is due.

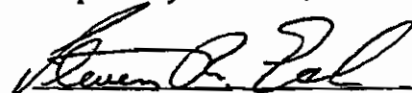
The Commissioner is hereby authorized to charge any additional fee due as required under 37 C.F.R. 1.17(p) by this paper to American Home Products

WYETH 002-000040

AHP-95011-1-C1
PATENT

Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

Respectfully submitted,



Steven R. Eck
Reg. No. 36,126

Dated: July 13, 1999

Telephone: (610) 902-2628

Enclosure: Form PTO-1449 with copies of references

WYETH 002-000041

file:///c:/APPS/preexam/correspondence/4.htm

#2

FORMALITIES LETTER



OC0000000499542

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark OfficeAddress: COMMISSIONER OF PATENT AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
09/488,629	01/20/2000	Deborah M. Sherman	AHP-95011-P2

Egon E Berg
American Home Products Corporation
Patent Law Department 2B
One Campus Drive
Parsippany, NJ 07054

Date Mailed: 03/20/2000

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given TWO MONTHS from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- Total additional claim fee(s) for this application is \$78.
 - \$78 for 1 independent claims over 3 .
- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of \$130 for a non-small entity, must be submitted with the missing items identified in this letter.
- The balance due by applicant is \$ 208.

A copy of this notice MUST be returned with the reply.

BW

T-C

Customer Service Center
Initial Patent Examination Division (703) 308-1202

PART 3 - OFFICE COPY

WYETH 002-000042

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WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

DATE

Patricia L. Kelly
April 19, 2000



03C0
AHP-95011 P2
PATENT
2 1/2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman et al.

Serial No.: 09/488,629

Filed: January 20, 2000

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, DC 20231

INFORMATION DISCLOSURE STATEMENT UNDER RULE 97

Sir:

With respect to the subject matter of the above-identified application; the applicants are aware of the references cited on the attached form PTO-1449 that were either cited by the applicants or by the Examiner during the prosecution of parent application Serial No. 08/964,328, filed November 5, 1997, of which the instant application is a continuation-in-part. Copies of these references are not enclosed.

Respectfully submitted,

A handwritten signature in dark ink, appearing to read "Steven R. Eck".

Steven R. Eck
Reg. No. 36,126

Dated: April 19, 2000

Telephone: (610) 902-2628

File
copy

Page 1 of 1

FORM PTO-1449 (REV. 2-32)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. AHP-95011-P2	SERIAL NO. 09/488,629
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)		APPLICANT Deborah M. Sherman et al.	
		FILING DATE January 20, 2000	GROUP AK 1615

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER							DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
JS	AA	3	9	5	4	9	5	9	8/75	Pedersen et al.	424	21	
JS	AB	4	3	6	9	1	7	2	1/83	Schor et al.	424	19	
	AC	4	1	3	8	4	7	5	2/79	McAinsh et al.	424	19	
	AD	4	3	8	9	3	9	3	6/83	Schor et al.	424	19	
	AE	4	9	6	6	7	6	8	10/90	Michelucci et al.	424	468	
	AF	5	5	0	6	2	7	0	4/96	Upton et al.	514	730	
JS	AG	4	5	3	5	1	8	6	8/86	Husbands et al.	564	336	
JS	AH	5	5	5	2	4	2	9	9/96	Wong et al.	514	415	
	AI												
	AJ												
	AK												

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER							DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
													YES	NO
JS	AL	0	6	5	4	2	6	4	11/94	EP	—	—		
	AM	0	6	6	7	1	5	0	1/95	EP	—	—		
	AN	9	4	2	7	5	8	9	12/94	WO	—	—		
JS	AO	9	7	3	7	6	4	0	10/97	WO	—	—		
JS	AP	0	7	9	7	9	9	1	10/97	EP	—	—		

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	AQ	
	AR	
	AS	
	AT	
	AU	
	AV	

EXAMINER JAMES M. SPEAR	DATE CONSIDERED 12-17-2000
-----------------------------------	--------------------------------------

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

WYETH 002-000044

WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

PATENT



Deborah M. Kelly
DATE May 12, 2000

IN THE UNITED STATES PATENT AND TRADEMARK
OFFICE

In re Patent Application of: Deborah M. Sherman
John C. Clark
John U. Lamer

Serial No.: 09/488,629

Filed: January 20, 2000

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, DC 20231

ATTENTION: Box Missing Parts

COMPLETION OF FILING
REQUIREMENTS

Sir:

This is in reply to the Notice to File Missing Parts of Application mailed March 20, 2000.

The original Declaration and Power of Attorney which was filed with the application was determined to be defective because the signatures were missing. A new original Declaration and a copy of Form PTO-1533 are attached.

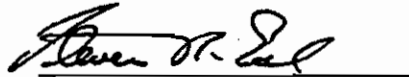
It was also noted that there is a total of four independent claims, and not six independent claims, as indicated on the Transmittal Letter filed with the application. Therefore, the Commissioner is hereby authorized to charge the fee of \$78.00 for the additional independent claim to American Home Products Corporation Deposit Account No. 01-1425.

Also enclosed is Request for a Corrected Filing Receipt.

As the applicants are other than a small entity, a surcharge fee of \$130.00 for filing a Declaration later than the filing date of the application is due pursuant to 37 CFR 1.16(e). The Commissioner is hereby authorized to charge any fees under 35 CFR 1.16 and 1.17 which may be required by this paper to American Home Products

Corporation Deposit Account No. 01-1425. Two additional copies of this paper are enclosed for this purpose.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Steven R. Eck", written over a horizontal line.

Steven R. Eck
Reg. No. 36,126

Dated: May 12, 2000
Telephone: (610) 902-2628

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING
DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS
FIRST CLASS MAIL IN A MANIFEST ENVELOPE ADDRESSED TO:
ASSISTANT COMMISSIONER FOR PATENTS,
WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

DATE

Raymond J. Kelly
May 12, 2000

Sector
AHP-95011 P2
PATENT



IN THE UNITED STATES PATENT AND TRADEMARK
OFFICE

In re Patent Application of:

Deborah M. Sherman
John C. Clark
John U. Lamer

Serial No.: 09/488,629

Filed: January 20, 2000

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, DC 20231

ATTENTION: Box Missing Parts

COMPLETION OF FILING
REQUIREMENTS

Sir:

This is in reply to the Notice to File Missing Parts of Application mailed
March 20, 2000.

The original Declaration and Power of Attorney which was filed with the
application was determined to be defective because the signatures were missing. A
new original Declaration and a copy of Form PTO-1533 are attached.

It was also noted that there is a total of four independent claims, and not six
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Therefore, the Commissioner is hereby authorized to charge the fee of \$78.00 for the
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Account No. 01-1425.

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As the applicants are other than a small entity, a surcharge fee of \$130.00 for
filing a Declaration later than the filing date of the application is due pursuant to 37
CFR 1.16(e). The Commissioner is hereby authorized to charge any fees under 35
CFR 1.16 and 1.17 which may be required by this paper to American Home Products

AHP-95011 P2
PATENT

Corporation Deposit Account No. 01-1425. Two additional copies of this paper are enclosed for this purpose.

Respectfully submitted;

A handwritten signature in dark ink, appearing to read "Steven R. Eck", is written over a horizontal line.

Steven R. Eck
Reg. No. 36,126

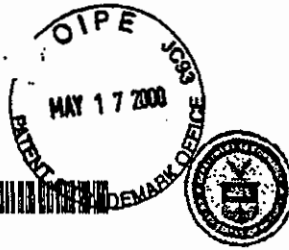
Dated: May 12, 2000
Telephone: (610) 902-2628

file:///c:/APPS/preexam/correspondence/3.htm

FORMALITIES LETTER



OC00000004999542

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark OfficeAddress: COMMISSIONER OF PATENT AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
09/488,629	01/20/2000	Deborah M. Sherman	AHP-95011-P2

Egon E Berg
American Home Products Corporation
Patent Law Department 2B
One Campus Drive
Parsippany, NJ 07054

Date Mailed: 03/20/2000

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given TWO MONTHS from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- Total additional claim fee(s) for this application is \$78.
 ■ \$78 for 1 independent claims over 3.
- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of \$130 for a non-small entity, must be submitted with the missing items identified in this letter.
- The balance due by applicant is \$ 208.

A copy of this notice MUST be returned with the reply.

HARRISON TC
Customer Service Center
Initial Patent Examination Division (703) 308-1202

PART 2 - COPY TO BE RETURNED WITH RESPONSE

05/19/2000 EHAMMOND 00000095 011425 09488629

01 FC:102 78.00 CH
02 FC:105 130.00 CH

WYETH 002-000232

AHP-95011 P2
PATENTDECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled Extended Release Formulation, the specification of which

(check one) X is attached hereto.

 was filed on as
Application Serial No.
and was amended on
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Priority Claimed
Yes No

<u> </u> (Number)	<u> </u> (Country)	<u> </u> (Day/Month/Year Filed)
-----------------------------------------	------------------------------------------	-------------------------------------------------------

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States Provisional Application(s) for Patent listed below:

<u>60/014,006</u> (Provisional Appln. No.)	<u>March 25, 1996</u> (Filing Date)
-----------------------------------------------	----------------------------------------

<u> </u> (Provisional Appln. No.)	<u> </u> (Filing Date)
---------------------------------------------------------	----------------------------------------------

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

AHP-95011 P2
PATENT

<u>08/821,137</u> (Application Serial No.)	<u>March 20, 1997</u> (Filing Date)	<u>Abandoned</u> (Status - Patented, pending, abandoned)
<u>08/964,328</u> (Application Serial No.)	<u>November 5, 1997</u> (Filing Date)	<u>Pending</u> (Status - Patented, pending, abandoned)

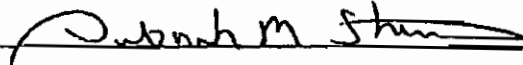
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

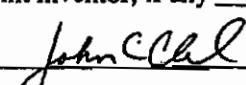
I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Egon E. Berg, Reg. No. 21,117, of One Campus Drive, Parsippany, New Jersey, 07054; and Rebecca R. Barrett, Reg. No. 35,152; Steven R. Eck, Reg. No. 36,126; Arnold S. Milowsky, Reg. No. 35,288; Michael R. Nagy, Reg. No. 33,432; George Tarnowski, Reg. No. 27,472; all of P.O. Box 8299, Philadelphia, Pennsylvania, 19101; and Daniel B. Moran, Reg. No. 41,204 of 401 N. Middletown Road, Pearl River, New York, 10965.

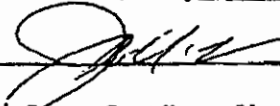
Address all telephone calls to Steven R. Eck at telephone number (610) 902-2628.

Address all correspondence to Egon E. Berg, American Home Products Corporation, Patent Law Department - 2B, One Campus Drive, Parsippany, New Jersey, 07054.

Full name of sole or first inventor Deborah M. Sherman
 Inventor's signature  26 Jan 00
 Date
 Residence 5 Belmont Avenue, Plattsburgh, New York, 12901
 Citizenship United States of America
 Post Office Address Same as residence

Full name of second joint inventor, if any John C. Clark
 Inventor's signature  27 Jan 00
 Date
 Residence 1 Rounds Drive, Peru, New York, 12972
 Citizenship United States of America
 Post Office Address Same as residence

AHP-95011 P2
PATENT

Full name of third joint inventor, if any John U. Lamer
Inventor's signature  27 Jan 00
Date
Residence 22 Farrar Street, St. Albans, Vermont, 05478
Citizenship United States of America
Post Office Address Same as residence

See change of Inventorship Papers Filed 04-13-01 Jpear
#7

I HEREBY CERTIFY THAT THE CORRESPONDENCE IS BEING
DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS
FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO:
ASSISTANT COMMISSIONER FOR PATENTS,
WASHINGTON, DC, 20231, ON THE DATE APPEARING BELOW.

DATE

Raymond J. Kelly
May 12, 2000



AHP-95011 P2
PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK
OFFICE**

In re Patent Application of:

Deborah M. Sherman
John C. Clark
John U. Lamer

Serial No.: 09/488,629

Filed: January 20, 2000

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, DC 20231

REQUEST FOR CORRECTED FILING RECEIPT

Sir:

Attached is a copy of the official Filing Receipt received from the USPTO in the above-identified application for which issuance of a corrected Filing Receipt is respectfully requested.

There is an error in the "Continuing Data As Claimed by Applicant". It should appear as follows:

Continuing Data as Claimed by Applicant

THIS APPLN IS A CIP OF 08/964,328	11/05/1997	ABN
WHICH IS A CIP OF 08/821,137	03/20/1997	ABN
AND CLAIMS THE BENEFIT OF 60/014,006	03/25/1996	ABN

The correction is not due to any error by applicant and no fee is due.

Respectfully submitted,

Steven R. Eck
Steven R. Eck
Reg. No. 36,136

Dated: May 12, 2000
Telephone: (610) 902-2628
Enclosure: Copy of filing receipt

WYETH 002-000236

file:///c:/APPS/preexam/correspondence/1.htm

CL. RADNOR/SIE

FILING RECEIPT



OC00000004999541

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark OfficeAddress: ASSISTANT SECRETARY AND
COMMISSIONER OF PATENT AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FL FEE REC'D	ATTY. DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/488,629	01/20/2000	1615	726	AHP-95011-P2	--	22	4

Egon E Berg
American Home Products Corporation
Patent Law Department 2B
One Campus Drive
Parsippany, NJ 07054

Date Mailed: 03/20/2000

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the PTO processes the reply to the Notice, the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Deborah M. Sherman, Pittsburgh, PA ;
John C. Clark, Peru, NY ;
John U. Lamer, St. Albans, VT ;

Continuing Data as Claimed by Applicant

THIS APPLICATION IS A CIP OF 08/964,328 11/05/1997 ABN
THIS APPLICATION IS A CIP OF 08/964,328 11/05/1997 ABN
THIS APPLICATION IS A CIP OF 08/964,328 11/05/1997 ABN
WHICH IS A CIP OF 08/821,137 03/20/1997 ABN
AND A CIP OF 08/821,137 03/20/1997 ABN
AND A CIP OF 08/821,137 03/20/1997 ABN
AND CLAIMS BENEFIT OF 60/014,006 03/25/1996
AND CLAIMS BENEFIT OF 60/014,006 03/25/1996
AND CLAIMS BENEFIT OF 60/014,006 03/25/1996

Foreign Applications

If Required, Foreign Filing License Granted 03/20/2000

Title

Extended release formulation

AM. HOME PROD. CORP.

MAR 31 2000

PATENT DEPT. RADNOR

WYETH 002-000237


**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/488,629	01/20/00	SHERMAN	D AHP-95011-P2

HM12/0104

Egon E Berg
American Home Products Corporation
Patent Law Department 2B
One Campus Drive
Parsippany NJ 07054

EXAMINER

SPEAR, J

ART UNIT

PAPER NUMBER

1615

DATE MAILED:

01/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/488,629	Applicant(s) SHERMAN, ET AL.
	Examiner JAMES-M. SPEAR	Group Art Unit 1615

☒ Responsive to communication(s) filed on Jan 20, 2000

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire THREE month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-22 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) 21 and 22 is/are allowed.

☒ Claim(s) 1, 12, 18, and 19 is/are rejected.

☒ Claim(s) 2-11, 13-17, and 20 is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2.5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Application/Control Number: 09/488,629

Page 2

Art Unit: 1615

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 18 and 19 contain the trademark/trade name
HYDROXYPROPYLMETHYLCELLULOSE TYPE 2208 and TYPE 2910 and
ETHYLCELLULOSE TYPE HG 2834. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to

WYETH 002-000240

Application/Control Number: 09/488,629

Page 3

Art Unit: 1615

identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a hydroxyalkylcellulose (hydroxypropylmethylcellulose) and ethylcellulose and, accordingly, the identification/description is indefinite. It is unclear as to what the type terminology is indicative of and how the various compounds differ based on the number notation.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over McAinsh et al U.S. 4,138,475 in view of Wong et al U.S. 5,552,429.

McAinsh et al shows a hard gelatin capsule comprised of spheroids coated with a mixture of ethylcellulose and hydroxypropylmethylcellulose. The active agent propranolol is blended with microcrystalline cellulose to formulate the core spheroid. See Abstract, example and claim 1.

The reference does not show venlafaxine. Wong et al is relied on for teaching extended release dosage forms comprised of the same ingredients as McAinsh et al including the drugs venlafaxine and propranolol. See column 4, lines 7-10, column 6, lines 54-55, column 7, lines 18-22, formulation 5. To use the venlafaxine of Wong et al in the McAinsh et al capsule with a reasonable expectation of success would have been obvious to one of ordinary skill in the art.

WYETH 002-000241

Application/Control Number: 09/488,629

Page 4

Art Unit: 1615

Given the teachings of the prior art it would be reasonable to expect that propranolol common to both McAinsh et al and Wong et al could be combined with venlafaxine in a sustained release dosage form to increase patient compliance when the need arises to administer both drugs. The motivation being a desire to obtain optimum drug efficacy over a prolonged period of time while reducing the total number of dosages required.

Claims 2-11, 13-17 and 20 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 1, 12, 18 and 19 are rejected.

Claims 21 and 22 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James M. Spear whose telephone number is (703) 308-2457. The examiner can normally be reached on Monday thru Friday from 6:30 A.M. to 3:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for this Group is (703) 305-3592 or 308-4556.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

WYETH 002-000242

Application/Control Number: 09/488,629

Page 5

Art Unit: 1615

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

James M. Spear


January 3, 2001

James M. Spear
JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

WYETH 002-000243

Notice of References Cited				Application No. 09/488,629		Applicant. SHERMAN, ET AL.	
				Examiner JAMES M. SPEAR		Group Art Unit 1615	
U.S. PATENT DOCUMENTS							
	DOCUMENT NO.	DATE	NAME			CLASS	SUBCLASS
A	4,138,475	2/1979	McAinsh, et al			424	19
B	5,552,429	9/1996	WONG, ET AL.			514	415
C							
D							
E							
F							
G							
H							
I							
J							
K							
L							
M							
FOREIGN PATENT DOCUMENTS							
	DOCUMENT NO.	DATE	COUNTRY	NAME		CLASS	SUBCLASS
N							
O							
P							
Q							
R							
S							
T							
NON-PATENT DOCUMENTS							
	DOCUMENT (Including Author, Title, Source, and Pertinent Pages)						DATE
U							
V							
W							
X							

Interview Summary

Application No. 09/488,629	Applicant(s) SHERMAN, ET AL.	
Examiner JAMES M. SPEAR	Group Art Unit 1615	

All participants (applicant, applicant's representative, PTO personnel):

(1) JAMES M. SPEAR (3) _____(2) REBECCA R. BARRETT (4) _____Date of Interview Feb 16, 2001Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:Agreement ☒ was reached. ☐ was not reached.Claim(s) discussed: ALL PENDING CLAIMS

Identification of prior art discussed:

Art of record.

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Discussed canceling claim one to overcome art rejection and amending claims 12, 18 and 19 to overcome 112 rejection.
The examiner would consider claims 21 and 22, amended to delete encapsulated, for allowability pending further search.
An amendment will follow.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

James M. Spear
JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

CERTIFICATE OF MAILING BY "EXPRESS" MAIL
 "EXPRESS MAIL" MAILING LABEL NUMBER BM74058701US
 DATE OF DEPOSIT February 16, 2001

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE BY "EXPRESS MAIL" POST OFFICE TO ADDRESSEE SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231

Judith A. Johnston

(TYPED OR PRINTED NAME OF PERSON MAILING PAPER OR FEE)

Judith A. Johnston
 (SIGNATURE OF PERSON MAILING PAPER OR FEE)



U.S. DEPARTMENT OF COMMERCE
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 Washington, D.C. 20231

Docket No.

HP-99811-P

PATENT

RECEIVED



In re Patent Application of D.M.Sherman; J.C.Clark & J.U.Lamer

Serial No. 09/488,629

Examiner J. Spear

Filed January 20, 2000

Group 1615

For Extended Release Formulation

CONFIRMATION NO. 4728

ASSISTANT COMMISSIONER FOR PATENTS
 Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

☐ No additional fee is required.

The fee has been calculated as shown below.

CLAIMS AS AMENDED						
(1)	(2) CLAIMS REMAINING AFTER AMENDMENT	(3)	(4) HIGHEST NO. PREVIOUSLY PAID FOR	(5) PRESENT EXTRA	(6) RATE	(7) ADDITIONAL FEE
TOTAL CLAIMS	25	MINUS	22	3	x \$18.	54.00
INDEP. CLAIMS	9	MINUS	6	3	x \$80.	240.00
MULTIPLE DEPENDENT CLAIMS	0		0	0	\$270.	0.00
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT						294.00

- * If the entry in Column 2 is less than the entry in Column 4, write "0" in Column 5.
 ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
 *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

- ☐ Fee for Terminal Disclaimer under 37CFR 1.20 (d) (\$110.00) is also transmitted herewith.
- ☐ Fee of \$_____ pursuant to 37 CFR 1.17(a) for extension of time under 37 CFR 1.136(a) is also transmitted herewith.
- ☒ Charge \$ 294.00 to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required by this paper to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

Rebecca R. Barrett
 Rebecca R. Barrett
 Reg. No. 35,152
 February 16, 2001

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
 "EXPRESS MAIL" MAILING LABEL NUMBER EM474058701US
 DATE OF DEPOSIT February 16, 2001



**U.S. DEPARTMENT OF COMMERCE
 Patent and Trademark Office**

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 POST OFFICE TO ADDRESSEE SERVICE UNDER 37 CFR 1.10 ON
 THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT
 COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231

Judith A. Johnston

(TYPED OR PRINTED NAME OF PERSON MAILING PAPER OR FEE)

Judith A. Johnston
 (SIGNATURE OF PERSON MAILING PAPER OR FEE)

Docket No. AHP-95011-P2
PATENT



In re Patent Application of D.M.Sherman; J.C.Clark & J.U.Lamer

Serial No. 09/488,629

Examiner J. Spear

Filed January 20, 2000

Group 1615

For Extended Release Formulation

CONFIRMATION NO. 4728

ASSISTANT COMMISSIONER FOR PATENTS
 Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

☐ No additional fee is required.

The fee has been calculated as shown below.

CLAIMS AS AMENDED						
(1)	(2) CLAIMS REMAINING AFTER AMENDMENT	(3)	(4) HIGHEST NO. PREVIOUSLY PAID FOR	(5) PRESENT EXTRA	(6) RATE	(7) ADDITIONAL FEE
TOTAL CLAIMS	25	MINUS	22	3	x \$18.	54.00
INDEP. CLAIMS	9	MINUS	6	3	x \$80.	240.00
MULTIPLE DEPENDENT CLAIMS	0		0	0	\$270.	0.00
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT						294.00

- * If the entry in Column 2 is less than the entry in Column 4, write "0" in Column 5.
 ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
 *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

- ☐ Fee for Terminal Disclaimer under 37CFR 1.20 (d) (\$110.00) is also transmitted herewith.
- ☐ Fee of \$_____ pursuant to 37 CFR 1.17(a) for extension of time under 37 CFR 1.136(a) is also transmitted herewith.
- ☒ Charge \$ 294.00 to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required by this paper to American Home Products Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

Rebecca R. Barrett

Rebecca R. Barrett
 Reg. No. 35,152
 February 16, 2001

USCOMM-DC 60425-P69

MP769-1N (12/00)

FORM PO-1083 (11-99)

WYETH 002-000251

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

"Express Mail" mailing label number EM4740587 JSDate of Deposit February 16, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, DC, 20231.

Judith A. Johnston

Name of Person Mailing Paper or Fee

Signature of Person Mailing Paper or Fee

AHP-95011-P2
PATENT

TECH CENTER 1600/2300

FEB 21 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman
John C. Clark
John U. Lamer

Serial No.: 09/488,629

Confirmation No.: 4728

Filed: January 20, 2000

Examiner: J. Spear

For: Extended Release Formulation

Group: 1615

Assistant Commissioner for Patents
Washington, D.C. 20231

*WPA
Supp
3-5-01*

REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.111

Sir:

This is in response to the Office Action issued in connection with this case. The Office Action has been carefully reviewed and the following response prepared. Please amend the application as follows:

In the Claims:

Please cancel Claim 1.

2 Please amend the claims as follows:

12. An extended release formulation [according to Claim 1] of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule [wherein the containing spheroids [are] comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

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12. (Amended) An extended release formulation according to Claim 2 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose [2208], and about 62% by weight of microcrystalline cellulose.

a2

17. (Amended) [A film coating composition] An extended release formulation according to Claim 2 wherein the film coating composition is [which is] comprised of about 85% by total weight of film coating of ethyl cellulose having 44.0 - 51.0% content of ethoxy groups, and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

18. (Amended) [A film coating composition] An extended release formulation according to Claim 2 [which] wherein the film coating composition is comprised of 85% by weight of ethyl cellulose having an ethoxy content of 44.0-51% and a viscosity of 50 cps for a 5% aqueous solution, [type HG 2834] and 15% by weight of hydroxypropylmethylcellulose having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12% [type 2910].

a3

19. (Amended) An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose [type 2208], coated with a quantity of a mixture comprised of 85% ethyl cellulose [type HG 2834] and 15% hydroxypropylmethylcellulose [type 2910] sufficient to give coated spheroids having a dissolution profile [which gives the desired release rate over a 24 hour period] in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time	Average % Venlafaxine HCl Released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

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In Claims 3, 4, ~~6~~ and 11, please delete "Claim 1" and insert --Claim 2-- therefor.

In Claim 8, please ~~delete~~ "Claim 6" and insert --Claim 2-- therefor.

In Claims 13, 14, 15, and 16, please ~~delete~~ "A composition" and insert --An extended release formulation-- therefor.

Please add the following new claims:

~~23~~ 23. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

~~24~~ 24. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

~~25~~ 25. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

~~26~~ 26. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need

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cont

thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient. *cl*

Remarks

Claims 1-22 were pending in this case. Applicants appreciate the Examiner's indication that Claims 21 and 22 are allowed and that Claims 2-11, 13-17 and 20 are allowable. Claims 1, 12, 18 and 19 were rejected. Claim 1 was cancelled by this paper, without prejudice to its presentation in a divisional application. Claim 2 was rewritten in independent form by incorporating the subject matter of Claim 1. Claims 3, 4, 6 and 11 were amended to depend from Claim 2 rather than from cancelled Claim 1. Claims 12, 18 and 19 were amended to delete reference to trademarks/-tradenames. Claim 19 was also amended to specifically enumerate the dissolution profile referenced in the claim. Claims 13-18 were amended to proper dependent form by conforming their preambles to that of Claim 2 from which Claims 13-18 depend. Claims 8-10 were amended to depend from Claim 2 rather than from Claim 6 (which depends from Claim 2). New Claims 23 through 26 were added. New Claims 23 through 26 are supported throughout the specification and particularly, for example, at page 3, lines 14-19. No change in claim scope is intended by these amendments.

Claims 12, 18 and 19 were rejected under 35 U.S.C. §112, second paragraph, because they recited trademarks or tradenames. Applicants have amended Claims 12, 18 and 19 to delete trademarks/names. Reference is made generically instead to hydroxypropylmethylcellulose or ethylcellulose as supported, for example, in Claim 2, and in the specification at Page 6, line 30 through Page 7, line 4. Claims 12, 18 and 19 should not be limited to the particular hydroxypropylmethylcellulose or ethylcellulose identified by the trademark/name.

Claim 1 was rejected under 35 U.S.C. §103(a). Claim 1 was cancelled, without prejudice to its presentation in a divisional application. Accordingly, this rejection is moot.

Claims 2-11, 13-17 and 20 were objected to as being dependent upon a rejected base claim. Claim 2 has been rewritten as an independent claim. Claims 3-

4 27

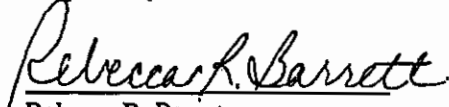
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PATENT

11, 13-17 and 20 have been amended so that they depend, directly or indirectly,
from allowable Claim 2. Accordingly, this objection should be withdrawn.

In view of the foregoing, Claims 2-26 are in condition ready for allowance.
An early and favorable Notice of Allowance is respectfully requested.

Respectfully submitted,


Rebecca R. Barret
Reg. No. 35,152

Dated: February 16, 2001

Telephone: (610)-902-2646

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WYETH 002-000256

HAND-CARRIED

AHP-95011 P2

PATENT

*7/ Petition
under 1.48(a)*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman, John C. Clark,
John U. Lamer

Serial No.: 09/488,629

Examiner: Spear J.

Filed: January 20, 2000

Group: 1615

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, D.C. 20231



25291

PATENT TRADEMARK OFFICE

*4-10-01
Approved
For Entry
open*

**AMENDMENT, PETITION AND FEE TO ADD
INVENTOR UNDER 37 CFR § 1.48 (a)**

1. This amendment and petition is to correct the incorrect original naming of inventor(s) in the declaration filed on January 20, 2000.
2. Please add the following previously unnamed person as an inventor of this application:

Stephen A. White

3. Attached is:

(a) A statement from Stephen A. White that the error occurred without deceptive intention on his part. 37 C.F.R. § 1.48(a)(1).

(b) a declaration by each of the actual inventor(s) as required by 37 C.F.R. 1.63 (or as permitted by §§ 1.42, 1.43 or 1.47). 37 C.F.R. §1.48(a)(2).

(c) written assent of the assignee (if any of the original inventors executed an assignment) 37 C.F.R. §1.48(a)(4).

04/18/2001 CWILLIAM 00000001 011425 09488629

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AHP-95011 P2
PATENT

4. Fee Payment (37 C.F.R. §1.17(i))
The fee required is paid as follows:
 X Charge Deposit Account 01-1425 the sum of \$130.00

Rebecca R. Barrett
Signature of Practitioner

Reg. No. 35,152

Rebecca R. Barrett
(type or print name of practitioner)

Tele. No. : (610) 902-2646

Date:

AHP-95011 P2
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman, John C. Clark,
John U. Lamer

Serial No.: 09/488,629

Examiner: Spear J.

Filed: January 20, 2000

Group: 1615

For: Extended Release Formulation

Confirmation No. 4728

Assistant Commissioner for Patents
Washington, D.C. 20231

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11:11:17

STATEMENT UNDER 37 CFR § 1.48 (a)(1)

I, Stephen A. White hereby state that the error in inventorship in the above-captioned case occurred without deceptive intent on my part.

I further declare that all statements made herein from my own knowledge are true and that all statements made on information and belief are believed to be true.

I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this patent application or any patent issuing thereon.

Further, declarant sayeth not.

Date:

10 Apr 01

Declarant



Stephen A. White

WYETH 002-000259

AHP-95011 P2
PATENTDECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is the invention entitled EXTENDED RELEASE FORMULATION, the specification of which

(check one) _____ is attached hereto.

X was filed on January 20, 2000 as
Application Serial No 09/488,629
and was last amended on February 16, 2001
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56 (a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Priority Claimed
Yes No

NONE
(Number) (Country) (Day/Month/Year Filed)

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States Provisional Application(s) for Patent listed below:

60/014,006 March 25, 1996
(Provisional Appln. No.) (Filing Date)

(Provisional Appln. No.) (Filing Date)

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

AHP-95011 P2
PATENT

<u>08/821,137</u> (Application Serial No.)	<u>3/20/97</u> (Filing Date)	<u>Abandoned</u> (Status - Patented, pending, abandoned)
<u>08/964,328</u> (Application Serial No.)	<u>11/5/97</u> (Filing Date)	<u>Abandoned</u> (Status - Patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Egon E. Berg, Reg. No. 21,117; of Five Giralda Farms, Madison, New Jersey, 07940; and Rebecca R. Barrett, Reg. No. 35,152; Steven R. Eck, Reg. No. 36,126; Arnold S. Milowsky, Reg. No. 35,288; Michael R. Nagy, Reg. No. 33,432; George Tarnowski, Reg. No. 27,472; all of P.O. Box 8299, Philadelphia, Pennsylvania, 19101; and Daniel B. Moran, Reg. No. P-41,204 of 401 N. Middletown Road, Pearl River, New York, 10965.

Address all telephone calls to Rebecca R. Barrett at
telephone number (610) 902-2646.

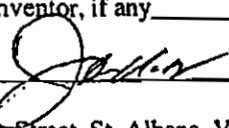
Address all correspondence to Egon E. Berg, American Home Products Corporation, Patent Law Department - 2B, Five Giralda Farms, Madison, New Jersey, 07940.

Full name of sole or first inventor Deborah M. Sherman
Inventor's signature *Deborah M. Sherman* 15 Mar 01
Date
Residence 5 Belmont Avenue, Plattsburgh, New York 12901
Citizenship United States of America
Post Office Address Same as residence

Full name of second joint inventor, if any John C. Clark
Inventor's signature *John C. Clark* 29 Mar 01
Date
Residence 375 Pleasant St., Peru, New York 12972
Citizenship United States of America
Post Office Address Same as Residence

AHP-95011 P2
PATENT

Full name of third joint inventor, if any John U. Lamer

Inventor's signature  22 Mar 01
Date

Residence 22 Farrar Street, St. Albans, Vermont 05478

Citizenship United States of America

Post Office Address Same as Residence

Full name of fourth joint inventor, if any Steven A. White

Inventor's signature  29 Mar 01
Date

Residence 309 Southwick Rd., Champlain, NY 12919

Citizenship United States of America

Post Office Address Same as Residence

AHP-95011PC2
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman, John C. Clark,
John U. Lamer

Serial No.: 09/488,629

Examiner: Spear J.

Filed: January 20, 2000

Group: 1615

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, D.C. 20231

**CONSENT OF ASSIGNEE TO
CHANGE OF INVENTORSHIP IN PATENT**

Sir:

American Home Products Corporation, owner by assignment of the above patent in the assignment recorded in the U.S. Patent and Trademark Office on March 7, 2001, Reel 011368 and Frame 0195, hereby consents to the amendment of the inventorship of this patent as requested in the accompanying papers.

AMERICAN HOME PRODUCTS CORPORATION

By: _____

Egon E. Berg
Vice President

Dated: April 3, 2001

WYETH 002-000263



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

TECH CENTER 1600/2900

APR 24 2001

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CHANGE OF ADDRESS/POWER OF ATTORNEY

FILE LOCATION 16C3 SERIAL NUMBER 09488629 PATENT NUMBER

THE CORRESPONDENCE ADDRESS HAS BEEN CHANGED TO CUSTOMER # 25291

THE PRACTITIONERS OF RECORD HAVE BEEN CHANGED TO CUSTOMER # 25291

THE FEE ADDRESS HAS BEEN CHANGED TO CUSTOMER # 25291

ON 04/03/01 THE ADDRESS OF RECORD FOR CUSTOMER NUMBER 25291 IS:

AMERICAN HOME PRODUCTS CORPORATION
PATENT SECTION
FIVE GIRALDA FARMS
MADISON NJ 07940-0874

AND THE PRACTITIONERS OF RECORD FOR CUSTOMER NUMBER 25291 ARE:

21117	22847	26942	27324	27472	27626	28049	28469	29520	29639
30637	31088	32245	32269	32703	32803	33365	33432	34210	34276
34614	35152	35288	36126	39206	41148	41204	41859	45822	

PTO INSTRUCTIONS: PLEASE TAKE THE FOLLOWING ACTION WHEN THE CORRESPONDENCE ADDRESS HAS BEEN CHANGED TO CUSTOMER NUMBER: RECORD, ON THE NEXT AVAILABLE CONTENTS LINE OF THE FILE JACKET, 'ADDRESS CHANGE TO CUSTOMER NUMBER'. LINE THROUGH THE OLD ADDRESS ON THE FILE JACKET LABEL AND ENTER ONLY THE 'CUSTOMER NUMBER' AS THE NEW ADDRESS. FILE THIS LETTER IN THE FILE JACKET. WHEN ABOVE CHANGES ARE ONLY TO FEE ADDRESS AND/OR PRACTITIONERS OF RECORD, FILE LETTER IN THE FILE JACKET. THIS FILE IS ASSIGNED TO GAU 1615.

PTO-FMD
TALBOT-1/97

WYETH 002-000264

Notice of AllowabilityApplication No.
09/488,629

Applicant(s)

SHERMAN, ET AL.

Examiner

JAMES M. SPEAR

Art Unit

1615

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course. THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS. This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to THE AMENDMENT FILED FEBRUARY 16, 2001.2. ☒ The allowed claim(s) is/are 2-26.3. ☐ The drawings filed on _____ are acceptable as formal drawings.4. ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).a) ☐ All b) ☐ Some* c) ☐ None of the:1. ☐ Certified copies of the priority documents have been received.2. ☐ Certified copies of the priority documents have been received in Application No. _____.3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

5. ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. THIS THREE-MONTH PERIOD IS NOT EXTENDABLE FOR SUBMITTING NEW FORMAL DRAWINGS, OR A SUBSTITUTE OATH OR DECLARATION. This three-month period for complying with the REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL is extendable under 37 CFR 1.136(a).

6. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.7. ☐ Applicant MUST submit NEW FORMAL DRAWINGS(a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached1) ☐ hereto or 2) ☐ to Paper No. _____.(b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.(c) ☐ including changes required by the attached Examiner's Amendment/Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

8. ☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any reply to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)1 ☐ Notice of References Cited (PTO-892)3 ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)5 ☐ Information Disclosure Statement(s) (PTO-1449), Paper No(s). _____7 ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material9 ☐ Other2 ☐ Notice of Informal Patent Application (PTO-152)4 ☐ Interview Summary (PTO-413), Paper No. _____6 ☐ Examiner's Amendment/Comment8 ☐ Examiner's Statement of Reasons for Allowance

James M. Spear
JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

ATTACHMENT TO AND MODIFICATION OF
NOTICE OF ALLOWABILITY (PTO-37)
(November, 2000)

NO EXTENSIONS OF TIME ARE PERMITTED TO FILE CORRECTED OR FORMAL DRAWINGS, OR A SUBSTITUTE OATH OR DECLARATION, notwithstanding any indication to the contrary in the attached Notice of Allowability (PTO-37).

If the following language appears on the attached Notice of Allowability, the portion lined through below is of no force and effect and is to be ignored¹:

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" of this Office action. Failure to comply will result in ABANDONMENT of this application. ~~Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).~~

Similar language appearing in any attachments to the Notice of Allowability, such as in an Examiner's Amendment/Comment or in a Notice of Draftperson's Patent Drawing Review, PTO-948, is also to be ignored.

¹ The language which is crossed out is contrary to amended 37 CFR 1.85(c) and 1.136. See "Changes to Implement the Patent Business Goals", 65 Fed. Reg. 54603, 54629, 54641, 54670, 54674 (September 8, 2000), 1238 Off. Gaz. Pat. Office 77, 99, 110, 135, 139 (September 19, 2000)



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

002001 HM42/0512
AMERICAN HOME PRODUCTS CORPORATION
PATENT SECTION
FIVE HUNTERDALE PARK
MADISON NJ 07940-0874

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/488,629	01/29/00	025	SPEAR, J	1615 05/09/01
First Named Applicant	SHEPMAN,	05 USC 154(b) term ext. =	0 Days.	

TITLE OF INVENTION EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPL. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1	AMP-95011-P2	474-061.000	614	UTILITY	NO \$1240.00	08/09/01

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

- If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
- If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

- Pay FEE DUE shown above, or
- File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PATENT AND TRADEMARK OFFICE COPY

PTOL-85 (REV. 10-96) Approved for use through 06/30/99. (0651-0033)

WYETH 002-000267

PART 8—ISSUE FEE TRANSMITTAL

Complete and mail this form together with applicable fees, to:

Box ISSUE FEE
Assistant Commissioner for Patents
Washington, D.C. 20231

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

025291 HM22/0509
AMERICAN HOME PRODUCTS CORPORATION
PATENT SECTION
FIVE GIRALDA FARMS
MADISON NJ 07940-0874

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

"Express Mail" Mailing Label Number EM7057642USDate of Deposit June 13, 2001

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE BY "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTS WASHINGTON, DC, 20231.

Rebecca R. Barrett
(TYPED OR PRINTED NAME OF PERSON MAILING PAPER OR FEE)
Rebecca R. Barrett
(SIGNATURE OF PERSON MAILING PAPER OR FEE)

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/488,629	01/20/00	025	SPEAR, J 1615	05/09/01
First Named Applicant	SHERMAN, 35 USC 154(b) term ext. = 0 Days.			

TITLE OF INVENTION EXTENDED RELEASE FORMULATION

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 AHP-95011-P2	424-461.000	G14	UTILITY	NO	\$1240.00	08/09/01

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). Use of PTO form(s) and Customer Number are recommended, but not required.

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB122) attached.

☐ "Fee Address" indication (or "Fee Address" indication form PTO/SB47) attached.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. Rebecca R. Barrett

2. _____

3. _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)
PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE
AMERICAN HOME PRODUCTS CORPORATION(B) RESIDENCE: (CITY & STATE OR COUNTRY)
MADISON, NEW JERSEY

Please check the appropriate assignee category indicated below (will not be printed on the patent)

☐ Individual ☒ Corporation or other private group entity ☐ government

4a. The following fees are enclosed (make check payable to Commissioner of Patents and Trademarks):

☐ Issue Fee☐ Advance Order - # of Copies _____

4b. The following fees or deficiency in these fees should be charged to:

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The COMMISSIONER OF PATENTS AND TRADEMARKS IS requested to apply the Issue Fee to the application identified above.

(Authorized Signature)

Rebecca R. Barrett

(Date)

6/13/01

NOTE: The Issue Fee will not be accepted from anyone other than the applicant, a registered attorney or agent, or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending on the needs of the individual case. Any comments on the amount of time required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND FEES AND THIS FORM TO: Box Issue Fee, Assistant Commissioner for Patents, Washington D.C. 20231

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PTOL-85B (REV.10-96) Approved for use through 06/30/99 FORM 0551-0003

Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

WYETH 002-000268

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

PATENT NO. : 4,535,186
DATED : August 13, 1985
INVENTOR(S) : G. E. Morris Husbands et al.
PATENT OWNER : American Home Products

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

FIVE YEARS

from the original expiration date of the patent, December 13, 2002, subject to the requirements of 35 U.S.C. § 41, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).



I have caused the seal of the Patent and Trademark Office to be affixed this 25th day of April 1996.

A handwritten signature in dark ink, reading "Bruce A. Lehman".

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

WYETH 002-000269

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"EXPRESS MAIL" MAILING LABEL NUMBER EL163893364USDATE OF DEPOSIT January 20, 2000

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U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address Only: Assistant Commissioner
for Patents
Washington, D.C. 20231

Case Docket No. AHP-95011-P2
PATENT

Sir:

Transmitted herewith for filing is the patent application of

Inventor: Deborah M. Sherman et al.For: Extended Release Formulation

This application is a:

- ☐ New Application ☒ CIP Application
- ☐ Divisional Application ☐ Continuation Application
of prior application No. 08/964,328. The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference.

Enclosed are:

0 sheets of drawing.

- ☐ Information Disclosure Statement.
- ☐ Preliminary Amendment.
- ☐ Signed statement attached deleting inventor(s) named in the prior application.

CLAIMS AS FILED				
(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) BASIC FEE \$690.00
TOTAL CLAIMS	22 -20 =	2	X 18.00	36.00
INDEPENDENT CLAIMS	6 -3 =	3	X 78.00	234.00
MULTIPLE DEPENDENT CLAIMS	0	0	280.00	0.00
TOTAL FILING FEE				960.00

☒ Please charge American Home Products Corporation Deposit Account No. 01-1425 in the amount of \$ 960.00. Two additional copies of this sheet are enclosed.

☒ The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this application to American Home Products Corporation Deposit Account No. 01-1425.

Steven R. Eck
Reg. No. 36,126

1c542 U.S. PTO
09/488629
01/20/00

WYETH 002-000325

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AHP-95011-1-C1
PATENT

DATE

Deborah J. Kelly
July 13, 1997



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman et al.

Serial No.: 08/964,328

Examiner: J. Spear

Filed: November 5, 1997

Group: 1615

For: Extended Release Formulation

Assistant Commissioner of Patents
Washington, DC 20231

SUPPLEMENTARY INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR 1.97(c)

Sir:

With respect to the subject matter of the above-identified application, the applicants have become aware of the following references, which may have relevance to the examination of the invention claimed.

WO 97/37640, published October 16, 1997; and
EP 0 797 991, published October 1, 1997

Form PTO-1449 and copies of the above references are enclosed.

The undersigned hereby states that each item contained in this Supplemental Information Disclosure Statement was cited in the PCT Search Report, dated June 1, 1997, in the counterpart PCT application. Since this Supplemental Information Disclosure Statement is being submitted with three months of the PCT Search Report, no fee is due.

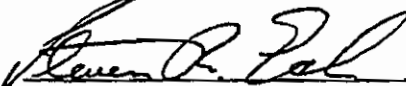
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WYETH 002-000326

AHP-95011-1-C1
PATENT

Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

Respectfully submitted,


Steven R. Eck
Reg. No. 36,126

Dated: July 13, 1999

Telephone: (610) 902-2628

Enclosure: Form PTO-1449 with copies of references

WYETH 002-000327

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AHP-95011-1-C1
PATENT



DATE

Raymond J. Kelly
July 13, 1999

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman et al.

Serial No.: 08/964,328

Examiner: J. Spear

Filed: November 5, 1997

Group: 1615

For: Extended Release Formulation

Assistant Commissioner of Patents
Washington, DC 20231

SUPPLEMENTARY INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR 1.97(c)

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The undersigned hereby states that each item contained in this Supplemental Information Disclosure Statement was cited in the PCT Search Report, dated June 1, 199, in the counterpart PCT application. Since this Supplemental Information Disclosure Statement is being submitted with three months of the PCT Search Report, no fee is due.

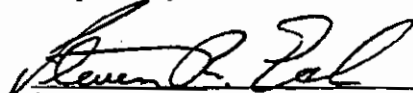
The Commissioner is hereby authorized to charge any additional fee due as required under 37 C.F.R. 1.17(p) by this paper to American Home Products

WYETH 002-000328

AHP-95011-1-C1
PATENT

Corporation Deposit Account No. 01-1425. Two additional copies of this sheet are enclosed.

Respectfully submitted,

A handwritten signature in dark ink, appearing to read "Steven R. Eck", written over a horizontal line.

Steven R. Eck
Reg. No. 36,126

Dated: July 13, 1999

Telephone: (610) 902-2628

Enclosure: Form PTO-1449 with copies of references

WYETH 002-000329

Freeform Search

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venlafaxine same method.clm.

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USPT,JPAB,EPAB,DWPI,TDBD	venlafaxine same method.ab.	4	<u>L1</u>

Freeform Search

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☐ EPO Abstracts Database
☐ Derwent World Patents Index
☐ IBM Technical Disclosure Bulletins

16 and microcrystalline

Term:

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Today's Date: 12/18/2000

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USPT,JPAB,EPAB,DWPI,TDBD	16 and microcrystalline	10	<u>L7</u>
USPT,JPAB,EPAB,DWPI,TDBD	15 and capsule	13	<u>L6</u>
USPT,JPAB,EPAB,DWPI,TDBD	venlafaxine.ab.	44	<u>L5</u>
USPT,JPAB,EPAB,DWPI,TDBD	venlafaxine same capsule	7	<u>L4</u>
USPT,JPAB,EPAB,DWPI,TDBD	11 and capsule.clm.	1	<u>L3</u>
USPT,JPAB,EPAB,DWPI,TDBD	11 and capsule	65	<u>L2</u>
USPT,JPAB,EPAB,DWPI,TDBD	venlafaxine	104	<u>L1</u>

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WYETH 002-000331

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Search Results -

Terms	Documents
venlafaxine same capsule	7

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☐ EPO Abstracts Database
☐ Derwent World Patents Index
☒ IBM Technical Disclosure Bulletins

Database:

venlafaxine same capsule

Refine Search:

Clear

Search History

Today's Date: 1/2/2001

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USPT,JPAB,EPAB,DWPI,TDBD	venlafaxine	104	<u>L2</u>
USPT,JPAB,EPAB,DWPI,TDBD	venlafaxine same microcrystalline	3	<u>L1</u>

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Generate Collection

L4: Entry 5 of 7

File: JPAB

Jan 13, 1999

PUB-NO: JP410007552A

DOCUMENT-IDENTIFIER: JP 10007552 A

TITLE: SUSTAINED RELEASE PHARMACEUTICAL PREPARATION

PUBN-DATE: January 13, 1998

INVENTOR-INFORMATION:

NAME

SHERMAN, DEBORAH

MARIE

ASSIGNEE-INFORMATION:

NAME

AMERICAN HOME PROD CORP

COUNTRY

N/A

APPL-NO: JP09060781

APPL-DATE: March 14, 1997

INT-CL (IPC): A61K 31/135; A61K 9/48; A61K 9/52

ABSTRACT:

PROBLEM TO BE SOLVED: To prepare the subject pharmaceutical preparation, comprising a hard gelatin capsule filled with a specific fine granule, capable of providing a desired dissolution profile and reducing adverse effects such as nausea or emesis and useful for treating depression.

SOLUTION: This sustained release pharmaceutical preparation comprises a hard gelatin capsule, filled with a therapeutically effective amount of a fine granule, containing (A) venlafaxine hydrochloride, (B) microcrystalline cellulose and (C) hydroxypropyl methyl cellulose and coated with (D) ethyl cellulose and the ingredient C. Furthermore, the fine granule is preferably composed of about 37.3wt.% ingredient A, about 0.5wt.% ingredient C and about 62.17wt.% ingredient B. The film coating composition is preferably composed of the ingredient D having 44.0-51.0wt.% content of ethoxy groups (15wt.% based on the total weight) and the ingredient C having 28.0-30.0wt.% content of methoxy groups and 7.0-12.0wt.% content of hydroxypropoxy groups (85wt.% based on the total weight).

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WEST**End of Result Set**

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L4: Entry 7 of 7

File: DWPI

Jun 29, 1999

DERWENT-ACC-NO: 1997-472908

DERWENT-WEEK: 199931

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TITLE: Encapsulated, extended release formulation of venlafaxine - used as anti-depressant, providing better control of blood plasma levels than conventional formulations

INVENTOR: SHERMAN, D M; CLARK, J C

PATENT-ASSIGNEE:

ASSIGNEE
AMERICAN HOME PROD CORP

CODE
AMHP

PRIORITY-DATA:

1996US-0014006

March 25, 1996

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
NZ 314442 A	June 29, 1999	N/A	000	A61K031/135
EP 797991 A1	October 1, 1997	E	009	A61K031/135
AU 9716400 A	October 2, 1997	N/A	000	A61K009/24
NO 9701206 A	September 26, 1997	N/A	000	A61K009/48
SK 9700301 A3	October 7, 1997	N/A	000	A61K009/48
CZ 9700772 A3	November 12, 1997	N/A	000	A61K031/045
JP 10007552 A	January 13, 1998	N/A	007	A61K031/135
HU 9700589 A2	September 29, 1997	N/A	000	A61K009/52
CA 2199778 A	September 25, 1997	N/A	000	A61K009/62
KR 97064599 A	October 13, 1997	N/A	000	A61K031/045
BR 9701304 A	September 29, 1998	N/A	000	A61K009/24
MX 9701873 A1	September 1, 1997	N/A	000	A61K031/135
ZA 9702403 A	November 25, 1998	N/A	014	A61J000/00

DESIGNATED-STATES: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV NL PT RO SE SI

CITED-DOCUMENTS: EP 112669; EP 639374 ; EP 654264 ; WO 9427589

APPLICATION-DATA:

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PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-NO
NZ 314442A	March 19, 1997	1997NZ-0314442	N/A
EP 797991A1	March 21, 1997	1997EP-0301937	N/A
AU 9716400A	March 20, 1997	1997AU-0016400	N/A
NO 9701206A	March 14, 1997	1997NO-0001206	N/A
SK 9700301A3	March 7, 1997	1997SK-0000301	N/A
CZ 9700772A3	March 13, 1997	1997CZ-0000772	N/A
JP10007552A	March 14, 1997	1997JP-0060781	N/A
HU 9700589A2	March 14, 1997	1997HU-0000589	N/A
CA 2139778A	March 12, 1997	1997CA-2199778	N/A
KR97064599A	March 14, 1997	1997KR-0008590	N/A
BR 9701304A	March 14, 1997	1997BR-0001304	N/A
MX 9701873A1	March 12, 1997	1997MX-0001873	N/A
ZA 9702403A	March 19, 1997	1997ZA-0002403	N/A

INT-CL (IPC): A61J 0/00; A61K 9/16; A61K 9/24; A61K 9/48; A61K 9/50; A61K 9/52; A61K 9/54; A61K 9/62; A61K 31/015; A61K 31/045; A61K 31/13; A61K 31/135; A61K 47/38

ABSTRACTED-PUB-NO: EP 797991A
BASIC-ABSTRACT:

An encapsulated, extended release formulation of venlafaxine hydrochloride comprises a hard gelatin capsule containing venlafaxine hydrochloride spheroids, microcrystalline cellulose and hydroxypropyl methylcellulose coated with ethyl cellulose and hydroxypropylmethyl cellulose. Also claimed is a film coating composition formed from ethyl cellulose (15 wt. %), ethoxy groups and hydroxypropylmethyl cellulose (85 wt. %).

USE - The formulation is used to provide a therapeutic blood plasma concentration of venlafaxine over 24 hours, with diminished incidences of nausea and emesis. The formulation provides a peak plasma level for 4-8 hours (claimed).

ADVANTAGE - The treatment eliminates the troughs and peaks of drug concentration in patients attending the therapeutic metabolism of a plurality of daily doses (claimed).

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: ENCAPSULATE EXTEND RELEASE FORMULATION ANTI DEPRESS CONTROL BLOOD PLASMA LEVEL CONVENTION FORMULATION

DERWENT-CLASS: A96 B05 P33

CPI-CODES: A03-A01; A03-A04A1; A03-C01; A12-V01; A12-W05; B04-C02A1; B04-C02A2; B10-B03B; B12-M10A; B12-M11C; B14-J01A1;

CHEMICAL-CODES:

Chemical Indexing M2 *01*

Fragmentation Code

G013 G030 G038 G111 G563 H1 H103 H181 H4 H401
H461 H5 H541 H8 M1 M123 M132 M210 M211 M272
M273 M281 M282 M312 M321 M332 M343 M373 M391 M414
M431 M510 M520 M531 M541 M640 M782 M903 M904 N103
P451 Q110 Q120 Q130 Q140

Markush Compounds

199744-05101-M

Chemical Indexing M1 *02*

Fragmentation Code

H4 H401 H481 H5 H521 H8 M210 M211 M272 M281
M313 M321 M331 M332 M342 M383 M391 M423 M431 M782

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M903 M904 N103 Q110 Q120 Q130 Q140 V713
Specific Compounds
06563M

ENHANCED-POLYMER-INDEXING:

Polymer Index [1.1] 018 ; R01852*R G3634 D01 D03 D11 D10 D23 D22 D31 D42 D50 D76
D86 F24 F29 F26 F34 H0293 P0599 G3623 Polymer Index [1.2] 018 ; ND01 ; Q9999 Q7250 ;
Q9999 Q7523 ; Q9999 Q8037 Q7987 Polymer Index [1.3] 018 ; B9999 B4795 B4773 B4740
Polymer Index [1.4] 018 ; Q9999 Q7114*R Polymer Index [2.1] 018 ; R01858 G3678 G3634 D01
D03 D11 D10 D23 D22 D31 D42 D50 D76 D92 F24 F34 H0293 P0599 G3623 ; R06563 G3678
G3634 G3623 P0599 D01 D03 D11 D10 D23 D22 D31 D42 D50 F24 F26 F34 H0293 Polymer
Index [2.2] 018 ; ND01 ; Q9999 Q7250 ; Q9999 Q7523 ; Q9999 Q8037 Q7987 Polymer Index
[2.3] 018 ; K9745*R Polymer Index [3.1] 018 ; R24033 G3714 P0599 D01 F70 Polymer Index
[3.2] 018 ; ND01 ; Q9999 Q7250 ; Q9999 Q7523 ; Q9999 Q8037 Q7987 Polymer Index [3.3] 018
; B9999 B3792 B3747

SECONDARY-ACC-NO:

CPI Secondary Accession Numbers: C1997-150386

SEARCHED			
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	461	"	"
	458	"	"
	459	"	"
	461	"	"
	457	"	"
	456	"	"
	462	"	"
Above To Date 05-07-01 jspear			

INTERFERENCE SEARCHED			
Class	Sub.	Date	Exmr.
424	495	5-7-01	jspear
	494	"	"
	461	"	"
	458	"	"
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	457	"	"
	456	"	"
	462	"	"

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	Date	Exmr.
WEST	12-18-00	jspear

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WYETH 002-000337

ISSUE SLIP STAPLE AREA (for additional cross references)

POSITION	INITIALS	ID NO.	DATE
FEE DETERMINATION	T. D.		2-2-00
O.I.P.E. CLASSIFIER			2-16-00
FORMALITY REVIEW	HA	11423	3-20-00
RESPONSE FORMALITY REVIEW		11423	5-24-00

INDEX OF CLAIMS

✓ Rejected N Non-elected
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 - (Through numeral)..... Canceled A Appeal
 + Restricted O Objected

Claim	Date
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WYETH 002-000338

CLAIMS ONLY							SERIAL NO.	FILING DATE
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CLAIMS								
	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT			
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TOTAL IND.	4	↓		↓		↓		
TOTAL DEP.	18	←		←		←		
TOTAL CLAIMS	22							

* MAY BE USED FOR ADDITIONAL CLAIMS OR ADMENDMENTS

FORM PYO-2022 (1-98)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

U.S. GPO: 1998-443-593/89152

WYETH 002-000339

PATENT APPLICATION FEE DETERMINATION RECORD					Application or Docket Number	
Effective December 29, 1999					09/488629	
CLAIMS AS FILED - PART I						
(Column 1)		(Column 2)				
FOR	NUMBER FILED	NUMBER EXTRA				
BASIC FEE						
TOTAL CLAIMS	22	minus 20 =	2			
INDEPENDENT CLAIMS	4	minus 3 =				
MULTIPLE DEPENDENT CLAIM PRESENT						
* If the difference in column 1 is less than zero, enter "0" in column 2						
CLAIMS AS AMENDED - PART II						
(Column 1)		(Column 2)		(Column 3)		
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA			
Total	*	Minus	**			
Independent	*	Minus	***			
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM						
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.						
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."						
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."						
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.						

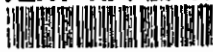
SMALL ENTITY TYPE <input checked="" type="checkbox"/>		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
	345.00	OR		690.00
X\$ 9=		OR	X\$18=	36
X39=		OR	X78=	
+130=		OR	+260=	
TOTAL		OR	TOTAL	726

SMALL ENTITY TYPE <input type="checkbox"/>		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X\$ 9=		OR	X\$18=	
X39=		OR	X78=	
+130=		OR	+260=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

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X\$ 9=		OR	X\$18=	
X39=		OR	X78=	
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SMALL ENTITY TYPE <input type="checkbox"/>		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X\$ 9=		OR	X\$18=	
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PATENT APPLICATION



09488629

JC542 U.S. PTO

09/488629



01/20/00

FEB 16 00 35

INITIALS _____

CONTENTS

	Date Received (Incl. C. of M.) or Date Mailed		Date Received (Incl. C. of M.) or Date Mailed
1. Application papers.	7/14/99	42.	
2. 1st FREE INDEX	3/20/00	43.	
3. 12 IDS 11K.	4/13/00	44.	
12-84. Rejection (3ma)	01/14/01	45.	
5. Examiner Interview Summary	2-16-01	46.	
6. AMTUA	2-16-01	47.	
7. Rejection into 1,43(a)	4-13-01	48.	
8. Change of address	4-24-01	49.	
5-78. Notice of allowance	07/09/01	50.	
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WYETH 002-000341

ALCOVERS AND COVER 1-800-366-8069
ALCOVERS PTD 1683-0 10 221 12 360 sheets

WYETH 002-000342

PTO-1683
(Rev. 7-96)

WYETH 002-000343

EXHIBIT 14

W 992376

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 28, 2003

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE
RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS
OF:

APPLICATION NUMBER: 09/884,412

FILING DATE: June 19, 2001

PATENT NUMBER: 6,419,958

ISSUE DATE: July 16, 2002



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS



H. L. Jackson
H. L. JACKSON
Certifying Officer

WYETH 002-000450

424	489	Subclass	Issue
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	O.I.E. 	PATENT DATE JUL 16 2002
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WYETH 002-000451



UNITED STATES PATENT AND TRADEMARK OFFICE

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UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
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Bib Data Sheet

CONFIRMATION NO. 2298

SERIAL NUMBER 09/884,412	FILING DATE 06/19/2001 RULE	CLASS 424	GROUP ART UNIT 1615	ATTORNEY DOCKET NO.
APPLICANTS Deborah M. Sherman, Plattsburg, NY; John C. Clark, Peru, NY; John U. Lamer, Albans, VT; Steven A. White, Champlain, NY;				
** CONTINUING DATA ***** THIS APPLICATION IS A DIV OF 09/488,629 01/20/2000 PAT 6,274,171 WHICH IS A CIP OF 08/964,328 11/05/1997 ABN WHICH IS A CIP OF 08/821,137 03/20/1997 ABN WHICH CLAIMS BENEFIT OF 60/014,006 03/25/1996				
** FOREIGN APPLICATIONS *****				
IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 08/10/2001				
Foreign Priority claimed <input type="checkbox"/> yes <input checked="" type="checkbox"/> no 35 USC 119 (a-d) conditions <input type="checkbox"/> yes <input checked="" type="checkbox"/> no <input type="checkbox"/> Met after met Verified and Acknowledged <i>Allowance</i> Examiner's Signature Initials		STATE OR COUNTRY NY	SHEETS DRAWING	TOTAL CLAIMS 3
INDEPENDENT CLAIMS 3				
ADDRESS 25291				
TITLE Extended release formulation, OF VENLAFAXINE HYDROCHLORIDE				
FILING FEE RECEIVED 710	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit	

WYETH 002-000452

AHP-95011-D1
PATENT

Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

NEW APPLICATION FOR TRANSMITTAL

Transmitted herewith for filing is the patent application of the following Inventor(s):
Deborah SHERMAN; John C. CLARK; John U. LAMER; Stephen A. WHITE;

For: Extended Release Formulation

1. Papers enclosed which are required for a filing date under 35 CFR 1.53(b):

- ☒ Pages of specification – 23 pages
☐ Sequence Listing – pages on:
☐ CD Rom or CD-R (2 copies); or
☐ paper
☒ Pages of claims – 4 pages
☒ Page(s) of abstract – 1 page
☐ Sheets of drawing – pages
☐ Formal
☐ Informal

2. Additional papers enclosed

- ☒ Information Disclosure Statement
☒ Form PTO-1449
☐ Citations
☐ Declaration of Biological Deposit
☐ Computer Readable Form of Sequence Listing
☐ Declaration Under 37 CFR 1.821(f)
☒ Other: Preliminary Amendment

3. Declaration

- ☒ Enclosed and executed by all inventor(s)
☐ Not enclosed or not executed by all inventor(s)

CERTIFICATE OF MAILING 37 CFR §1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EM474058074US addressed to the Commissioner for Patents, Box Patent Application, Washington, DC 20231.

June 19, 2001
Date

Mary Ellen Fiala
Mary Ellen Fiala

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4. Assignment

An assignment of the invention to:

American Home Products Corporation
 Five Giralda Farms
 Madison, NJ 07054-0874

- ☒ was made in the prior application and recorded in PTO.
- ☐ is attached under separate Recordation Form Cover Sheet.
- ☐ will follow.

5. Filing Fee Calculation

CLAIMS				
(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA x RATE		(4) BASIC FEE
				\$710.00
TOTAL CLAIMS	3	0	x \$ 18.00	0.00
INDEPENDENT CLAIMS	3	0	x \$ 80.00	0.00
MULTIPLE DEPENDENCY FEE	0		\$ 270.00	0.00
Total Filing Fee:				\$710.00

6. Method of Payment of Fees:

Charge American Home Products Corporation Deposit Account No. 01-1425 in the amount of \$710.00.

A duplicate of this transmittal is attached.

7. Instructions as to Overpayment:

Credit any overpayment to Deposit Account No. 01-1425.

8. General Authorization:

During the pendency of this application treat any reply requiring a petition for extension of time for its timely submission as containing a request therefor for the appropriate length of time. The Commissioner is hereby authorized to charge all required extension of time fees during the entire pendency of this application to Deposit Account No. 01-1425.

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9. Authorization to Charge Additional Fees

- ☒ The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Deposit Account No. 01-1425
- ☒ 37 CFR 1.16(a), (f), or (g) filing fees
- ☒ 37 CFR 1.16(b), (c), and (d) presentation of extra claims
- ☒ 37 CFR 1.16(e) surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application.
- ☒ 37 CFR 1.17 application processing fees

10. Relate back (35 USC 119(e)).

- ☐ Amend the Specification by inserting before the first line the sentence:

—This application claims priority from copending provisional application(s) serial number 60/ filed on .

11. Request and Certification Under 35 U.S.C 122(b)(2)(B)(i).

- ☐ A request not to publish this application and certification under 35 U.S.C. 122(b)(2)(B)(i) is attached.

12. Correspondence Address and Telephone Number

SEND CORRESPONDENCE TO:

Customer Number: 25291

Ms. Kay E. Brady

Patent Law Department

American Home Products Corporation

Five Giralda Farms

Madison, NJ 07940-0874

Bar Code:



25291

PATENT TRADEMARK OFFICE

DIRECT ALL TELEPHONE CALLS TO:

Name: Rebecca R. Barrett

Tel. No. 610-902-2646

13. ☒ Return Receipt Postcard is attached.

Rebecca R. Barrett
Rebecca R. Barrett

Reg. No. 35,152

American Home Products Corporation
Patent Law Department
Five Giralda Farms
Madison, NJ 07940-0874
Tel. No. (973) 683-2130

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EXTENDED RELEASE FORMULATION

INSAI ¹⁹¹ ~~This application continuation-in-part of Application Serial No. 08/964,328, filed November 5, 1997, which is a continuation-in-part of copending Application No. 08/821,137, filed March 20, 1997, which, in turn, claims priority from Provisional Application No. 60/014,006 filed March 25, 1996.~~

Background of the Invention

10 Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting
15 mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it
20 available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in US patent 4,966,768. US patent 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium
25 carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage
30 forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to

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form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. US patent 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propranolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in US patent 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

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Brief Description of the Invention

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a
5 twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time
10 profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release
venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine
15 hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a
threshold therapeutic level of the drug during the entire twenty-four period. In
20 contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in
25 need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that
30 attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was

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greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of

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total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

5 Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70 % to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of
10 hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

15 Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to
20 about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount
25 of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

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Detailed Description of the Invention

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19-24% and a hydroxypropoxy content of 4-13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis.

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Preferably the ethyl cellulose has a ethoxy content of 44.0-51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12%. The ethyl cellulose used herein is Aqualon
5 HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without
10 changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2-5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the
15 hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50-55°C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine
20 proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70%
25 dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone,
30 methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which

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could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

5

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

10

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

15

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

20

Example No. 1.

Venlafaxine Hydrochloride Extended Release Capsules

25

A mixture of 44.8 parts (88.4 % free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

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Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

- 5 To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

10 The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

Example No. 2

- 15 Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

Example No. 3

- 20 Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

Example No. 4

- 25 Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

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In the foregoing failed experiments and in Examples 1-4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an
5 hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this
10 invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5 % (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.
15

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6 % (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2
20 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified
30 water at 37°C.

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Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of
5 uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

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Table 1 Acceptable Coated Spheroid Dissolution Rates	
<u>Time (hours)</u>	<u>Average % Venlafaxine HCl released</u>
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into
15 pharmaceutically acceptable capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form
20 and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified.
25 The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules

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are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

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$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

10 where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

15 Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride
20 according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

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Table 2
Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended
release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 x 75 mg (ER)capsules (q 24 hr)	1 x 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

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Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

Table 3.

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20°C until analysis could be completed.

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To 1 mL of each plasma sample in a plastic tube was added 150 μ L of a stock internal standard solution (150 μ g/mL). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μ L portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μ L samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm x 4.6 mm, 5 μ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

Example No. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in

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combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

10 The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

Example No. 6

20 Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Kentucky 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/speronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Maryland 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

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<u>Ingredient</u>	<u>% (w/w)</u>
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns:

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<u>Time/hr</u>	<u>% Dissolved 16.5% / 5%</u>	<u>% Dissolved 16.5% / 7%</u>
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

Example No. 7

10 A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcrystalline cellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

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<u>Time/hr</u>	<u>% Dissolved 8.25% / 5%</u>
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

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What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.
2. An extended release formulation according to Claim 1 wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.
3. An extended release formulation according to Claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.
4. An extended release formulation according to Claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.
5. An extended release formulation according to Claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

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6. An extended release formulation according to Claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1 % to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose,

5

7. An extended release formulation according to Claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl-cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP

10

8. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose

15

9. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

20

10. An extended release formulation according to Claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

25

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to Claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

30

<u>Time (hours)</u>	<u>Average % Venlafaxine HCl released</u>
2	<30
4	30-55

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8
12
24

55-80
65-90
>80

- 5 12. An extended release formulation according to claim 2 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62% by weight of microcrystalline cellulose.
- 10 13. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).
- 15 14. A composition according to claim 2 wherein the film coating comprises 6-8% by weight of total weight.
- 20 15. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).
- 25 16. A composition according to claim 2 wherein film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.
- 30 17. A film coating composition according to Claim 2 which is comprised of about 85% by total weight of film coating of ethyl cellulose having a 44.0-51.0% content of ethoxy groups, and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

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18. A film coating composition according to Claim 2 which is comprised of 85% by weight of ethyl cellulose type HG 2834 and 15% by weight of hydroxypropylmethylcellulose type 2910.

5 19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 85% ethyl cellulose type HG 2834 and 15% hydroxypropylmethylcellulose type 2910 sufficient to give coated spheroids having a
10 dissolution profile which gives the desired release rate over a 24 hour period.

20. An extended release formulation of venlafaxine hydrochloride according to Claim 2 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

15 21. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level
20 of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of
25 venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

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also B1

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ABSTRACT OF THE DISCLOSURE

EXTENDED RELEASE FORMULATION

5 This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the
10 invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

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PATENTDECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is the invention entitled EXTENDED RELEASE FORMULATION, the specification of which

(check one) _____ is attached hereto.

X was filed on January 20, 2000 as
Application Serial No 09/488,629
and was last amended on February 16, 2001
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56 (a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Priority Claimed
Yes No

NONE
(Number) (Country) (Day/Month/Year Filed)

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States Provisional Application(s) for Patent listed below:

60/014,006 March 25, 1996
(Provisional Appln. No.) (Filing Date)

(Provisional Appln. No.) (Filing Date)

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

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<u>08/821,137</u>	<u>3/20/97</u>	<u>Abandoned</u>
(Application Serial No.)	(Filing Date)	(Status - Patented, pending, abandoned)

<u>08/964,328</u>	<u>11/5/97</u>	<u>Abandoned</u>
(Application Serial No.)	(Filing Date)	(Status - Patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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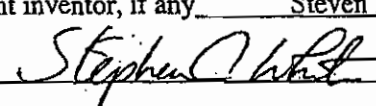
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002-000481

PATENT APPLICATION SERIAL NO. 09-884412

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

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*U.S. GPO: 2000-468-987/39595

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Deborah M. Sherman, John C. Clark,
John U. Lamer, Stephen A. White

Serial No.:
(Div. of USSN 09/488,629)

Examiner:

Filed: Herewith

Group:

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to issuance of an Office Action in this case, please amend the application as follows:

In the Application:

At page 1, line 3, please delete "This application continuation-in-part of Application Serial No. 08/964,328, filed November 5, 1997, which is a continuation-in-part of copending Application No. 08/821,137, filed March 20, 1997, which, in turn, claims priority from Provisional Application No. 60/014,006 filed March 25, 1996" and insert - "This application is a divisional application of Serial No. 09/488,629, filed January 20, 2000, ^{US 6,274,171} which is a continuation-in-part of Application Serial No. 08/964,328, filed November 5, 1997, now abandoned, which is a continuation-in-part of Application No. 08/821,137, filed March 20, 1997, now abandoned, which claims priority from Provisional Application No. 60/014,006 filed March 25, 1996" - .

In the Claims:

Cancel Claims 2-22 without prejudice.

Add new Claims 23-24 as follows:

- 128 A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an

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extended release formulation that provides a peak blood plasma level of venlafaxine in from about 4 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

A2
canceled

24. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 4 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient. - -

In view of the foregoing, Applicants respectfully maintain that Claims 1 and 23-24 are in condition ready for allowance and respectfully request an early and favorable Notice of Allowance.

Respectfully submitted,

Rebecca R. Barrett
Rebecca R. Barrett
Reg. No. 35,152

Dated: *June 19, 2001*
Telephone: (610) 902-2646

RECEIVED
JUN 20 2001

Docket No: 95011-1-D1

Patent

3

JCS78 U.S. PTO
09/884412
06/15/90IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Deborah M. Sherman et al.
Serial No.: Not Yet Known Group Art No.: 1615
Filed: Herewith Examiner:
For: Extended Release Formulation
Confirmation No.:
Customer Number: 25291

Assistant Commissioner for Patents
Washington, DC 20231

INFORMATION DISCLOSURE STATEMENT1. Preliminary Statements

In accordance with 37 CFR 1.97 and 1.98, Applicants submit herewith patents, publications, or other information of which they are aware, which they believe may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 CFR 1.56. This Information Disclosure Statement is not to be construed as a representation that: (i) a search has been made; (ii) the information is material to the examination of this application; (iii) additional information material to the examination of this application does not exist; (iv) the information, protocols, results and the like reported by third parties are accurate or enabling; or (v) the information constitutes prior art to the subject invention.

CERTIFICATE OF MAILING 37 CFR §1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EM474058074US addressed to the Assistant Commissioner for Patents, Washington, DC 20231.

June 19, 2001
Date

Mary Ellen Fiala
Mary Ellen Fiala

Docket No: 95011-1-D1

Patent

2. Identification of Time of Filing

This Information Disclosure Statement

- a. ☒ is filed within three months of the filing date of the application.
- b. ☐ is filed before the mailing date of a first Office Action on the merits.
- c. ☐ is filed before the mailing date of a first Office Action after the filing of a request for continued examination under 37 CFR 1.114.
- d. ☐ is filed after the period specified in 2(a), 2(b) or 2(c) above, but before the mailing date of a final action under 37 CFR 1.311. This statement includes a certification under 37 CFR 1.97(e) or the fee set forth in 37 CFR 1.17(p).
- e. ☐ is filed after the mailing date of a final action or Notice of Allowance but before payment of the issue fee. This statement includes (i) a certification under 37 CFR 1.97(e), and (ii) the fee set forth in 37 CFR 1.17(p).

3. ☐ Certification under 37 CFR 1.97(e)
The undersigned attorney certifies

- a. ☐ that each item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the statement, or
- b. ☐ that no item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application or, to the knowledge of the person signing the certification after making reasonable inquiry, was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the statement.
- c. ☐ The undersigned attorney certifies that each item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and was not received by any individual designated in 37 CFR 1.56(c) more than thirty (30) days prior to the filing of the statement.

☐ Newly Cited Information
A legible copy of the patents, publications or other information cited on the attached form PTO 1449 is enclosed, except that no copy of a pending U.S. application is enclosed.

☒ Previously Cited Information
No copy of the patents, publications or other information cited on the attached form PTO-1449 is enclosed because it has been previously cited by or submitted to the Office in a prior application which is relied upon for an earlier filing date under 35 USC 120.
Prior application is Serial Number 09/488,620, filed on January 20, 2000 of Sherman et al. for Extended Release Formulation..

Docket No: 95011-1-D1
Patent

- ☐ Concise Explanation
Documents cited above which are not in the English Language
- a. ☐ have been explained in the specification.
- b. ☐ have an abstract (or other concise explanation) in English enclosed or if readily available a translation into English of the document is enclosed.

Form PTO-1449 is enclosed in duplicate.

- ☐ Fees
- ☐ Fee for filing under 37 CFR 1.97(c) or (d) Fee: \$0.00

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Rebecca R. Barrett

Rebecca R. Barrett
Reg. No. 35,152

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Patent Law Department
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Madison, NJ 07940-0874
Tel. No. (610) 902-2646



25291

PATENT TRADEMARK OFFICE

#3

FORM PTO-1449 (REV. 2-32)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. AHP-95011-D1	SERIAL NO. Not Yet Known
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)		APPLICANT Deborah M. Sherman et al.	
		FILING DATE Not Yet Known	GROUP 1615

10979 U.S. PTO
09/884412
06/19/01

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
JS	AA	3 9 5 4 9 5 9	8/75	Pedersen			
↑	AB	4 3 6 9 1 7 2	1/83	Schor et al.			
	AC	4 1 3 8 4 7 5	2/79	McAinsh et al.			
	AD	4 3 8 9 3 9 3	6/83	Schor et al.			
	AE	4 9 6 6 7 6 8	10/90	Michelucci et al.			
	AF	5 5 0 6 2 7 0	4/96	Upton et al.			
↓	AG	4 5 3 5 1 8 6	8/86	Husbands et al.			
JS	AH	5 5 5 2 4 2 9	9/96	Wong et al.			
	AI						
	AJ						
	AK						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO
JS	AL	0 6 5 4 2 6 4	11/94	EP			
↑	AM	0 6 6 7 1 5 0	1/95	EP			
	AN	9 4 2 7 5 8 9	12/94	WO			
↓	AO	9 7 3 7 6 4 0	10/97	WO			
JS	AP	0 7 9 7 9 9 1	10/97	EP			

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

AQ	
AR	
AS	
AT	
AU	
AV	

EXAMINER: JAMES M. SPEAR DATE CONSIDERED 01-13-2002

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

WYETH 002-000488



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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,412	06/19/2001	Deborah M. Sherman		2298

25291 7590 01/14/2002

AMERICAN HOME PRODUCTS CORPORATION
 FIVE GIRALDA FARMS
 PATENT LAW
 MADISON, NJ 07940

EXAMINER

SPEAR, JAMES M

ART UNIT

PAPER NUMBER

1615

DATE MAILED: 01/14/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action SummaryApplication No.
09/884,412Applicant(s)
SHERMAN, ET ALExaminer
JAMES M. SPEARArt Unit
1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for ReplyA SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE THREE MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jun 19, 2001
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 23, and 24 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 23, and 24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892) 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 19) ☐ Notice of Informal Patent Application (PTO-152)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3 20) ☐ Other: _____

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Art Unit: 1615

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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Claims 23 and 24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20 and 21 of U.S. Patent No. 6,274,171. Although the conflicting claims are not identical, they are not patentably distinct from each other because while the claims of the patent require an encapsulated dosage form, to administer the extended release formulation in an unencapsulated form would have been obvious to one of ordinary skill in the art. The encapsulation is a means for containing the extended release dosage form. Since the capsule does not provide the means for extended release, it would be reasonable to expect one skilled in the art would modify the dosage form and administer the venlafaxine spheroids as unencapsulated dosages. The motivation being to optimize patient compliance and convenience of administration. Individuals having difficulty swallowing capsules would be more apt to comply with a dosage regimen when the formulation is unencapsulated and therefore easier to swallow.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

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patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over
McAinsh et al US 4,138,475 in view of Wong et al US 5,552,429.

McAinsh et al shows a hard gelatin capsule comprised of spheroids coated with a mixture of ethylcellulose and hydroxypropylmethylcellulose. The active agent propranolol is blended with microcrystalline cellulose to form a core spheroid. See Abstract, the example and claim 1. The sustained release results from the coating applied to the individual spheroids. The reference does not show venlafaxine. Wong et al is relied on for teaching extended release dosage forms comprised of the same ingredients as McAinsh et al including the drugs venlafaxine and propranolol. See column 4, lines 7-10, column 6, lines 54-55, column 7, lines 18-22, formulation 5. To use the venlafaxine of Wong et al in the McAinsh et al capsule, coated for sustained release, with a reasonable expectation of success would have been obvious to one of ordinary skill in the art. It would be reasonable to expect that propranolol common to both McAinsh et al and Wong et al could be combined with venlafaxine in a sustained release dosage form to increase patient

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compliance when the need arises to administer both drugs. The resulting combination dosage form would provide optimum drug efficacy over a prolonged period of time while reducing the total number of dosages required.

Claims 1, 23 and 24 are rejected. Claims 2-22 have been canceled.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James M. Spear whose telephone number is (703) 308 2457. The examiner can normally be reached on Monday thru Friday from 6:30 AM to 3 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 305 3592 or 308 4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308 1235.

James M. Spear January 13, 2002

James M. Spear
JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615

WYETH 002-000494

Notice of References CitedApplicant/Patent
SHERMAN, ET ALApplication/Control No.
09/884,412Examiner
JAMES M. SPEARArt Unit
1615

Page 1 of 1

U.S. PATENT DOCUMENTS

	Document Number Country Code-Number-Kind Code	Date MM-YYYY ¹	Name	Classification ²	
A	4,138,475	2/1979	McAINSH, ET AL	424	.19
B	5,552,429	9/1996	WONG, ET AL	514	415
C	6,274,171	8/2001	SHERMAN, ET AL	424	461
D					
E					
F					
G					
H					
I					
J					
K					
L					
M					

FOREIGN PATENT DOCUMENTS

	Document Number Country Code-Number-Kind Code	Date MM-YYYY ¹	Country	Name	Classification ²	
N						
D						
P						
Q						
R						
S						
T						

NON-PATENT DOCUMENTS

	Include, as applicable: Author, Title, Date, Publisher, Edition or Volume, Pertinent Pages
U	
V	
W	
X	

¹ A copy of this reference is not being furnished with this Office action. See MPEP § 707.05(a).¹ Dates in MM-YYYY format are publication dates.² Classifications may be U.S. or foreign.



US006274171B1

(12) **United States Patent**
Sherman et al.

(10) Patent No.: **US 6,274,171 B1**
 (45) Date of Patent: **Aug. 14, 2001**

(54) **EXTENDED RELEASE FORMULATION OF
 VENLAFAXINE HYDROCHLORIDE**

(75) Inventors: **Deborah M. Sherman, Plattsburgh;
 John C. Clark, Peru, both of NY (US);
 John U. Lamer, St. Albans, VT (US);
 Steven A. White, Champlain, NY (US)**

(73) Assignee: **American Home Products
 Corporation, Madison, NJ (US)**

(*) Notice: Subject to any disclaimer, the term of this
 patent is extended or adjusted under 35
 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/488,629**

(22) Filed: **Jan. 20, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/964,328, filed on
 Nov. 5, 1997, now abandoned, which is a continuation-in-
 part of application No. 08/821,137, filed on Mar. 20, 1997,
 now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25,
 1996.

(51) Int. Cl.⁷ **A61K 9/52; A61K 9/54;
 A61K 9/62**

(52) U.S. Cl. **424/461; 424/457; 424/458;
 424/459; 514/781; 514/962**

(58) Field of Search **424/495, 494,
 424/461, 458, 459, 457, 456, 462**

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,954,959 5/1976 Pedersen 424/21

4,138,475 * 2/1979 McAlinsh et al. 424/19
 4,369,172 1/1983 Schor et al. 424/19
 4,389,393 6/1983 Schor et al. 424/19
 4,535,186 8/1985 Husbands et al. 564/336
 4,966,768 10/1990 Michelucci et al. 424/468
 5,506,270 4/1996 Upton et al. 514/730
 5,552,429 * 9/1996 Wong et al. 514/415

FOREIGN PATENT DOCUMENTS

0654264 11/1994 (EP) .
 0667150 1/1995 (EP) .
 0797991 10/1997 (EP) .
 9427589 12/1994 (WO) .
 9737640 10/1997 (WO) .

* cited by examiner

Primary Examiner—James M. Spear

(74) Attorney, Agent, or Firm—Rebecca R. Barrett

(57) ABSTRACT

This invention relates to a 24 hour extended release dosage
 formulation and unit dosage form thereof of venlafaxine
 hydrochloride, an antidepressant, which provides better con-
 trol of blood plasma levels than conventional tablet formu-
 lations which must be administered two or more times a day
 and further provides a lower incidence of nausea and vom-
 iting than the conventional tablets. More particularly, the
 invention comprises an extended release formulation of
 venlafaxine hydrochloride comprising a therapeutically
 effective amount of venlafaxine hydrochloride in spheroids
 comprised of venlafaxine hydrochloride, microcrystalline
 cellulose and, optionally, hydroxypropylmethylcellulose
 coated with a mixture of ethyl cellulose and hydroxypropyl-
 methylcellulose.

25 Claims, No Drawings

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EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

This application continuation-in-part of Application Ser. No. 08/964,328, filed Nov. 5, 1997 abandoned, which is a continuation-in-part of Application Ser. No. 08/821,137, filed Mar. 20, 1997 abandoned, which, in turn, claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid

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increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally,

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hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride is polymorphic. Of the forms

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isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19-24% and a hydroxypropoxy content of 4-13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0-51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2-5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50-55° C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70% dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

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Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Six 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

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EXAMPLE NO. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1-4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hult and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF; optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%, w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates	
Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable

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capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(Ar)(Wr)(S)(V1)(0.884)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule			
Time (hours)	75 mg (IR) tablet (q 12 h)	2 x 75 mg (ER) capsules (q 24 hr)	1 x 150 mg (ER) capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		

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TABLE 2-continued

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule			
Time (hours)	75 mg (IR) tablet (q 12 h)	2 x 75 mg (ER) capsules (q 24 hr)	1 x 150 mg (ER) capsules (q 24 h)
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hours intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/mL, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/mL, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level			
Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As

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quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20° C. until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 μ L of a stock internal standard solution (150 μ g/mL). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μ L portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μ L samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm \times 4.6 mm, 5 μ ; column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model

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FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Ky. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/speronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns

Time/hr	% Dissolved 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

EXAMPLE NO. 7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing spheroids comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

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2. An extended release formulation of venlafaxine hydrochloride according to claim 1 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

3. An extended release formulation according to claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

4. An extended release formulation according to claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. An extended release formulation according to claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1% to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

7. An extended release formulation according to claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. An extended release formulation according to claim 1 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

9. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

10. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80

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-continued

Time (hours)	Average % Venlafaxine HCl released
12	65-90
24	>80

12. An extended release formulation according to claim 1 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose, and about 62% by weight of microcrystalline cellulose.

13. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

14. An extended release formulation according to claim 1 wherein the film coating comprises 6-8% by weight of total weight.

15. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

16. An extended release formulation according to claim 1 wherein the film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

17. An extended release formulation according to claim 1 wherein the film coating composition is comprised of about 85% by total weight of film coating of ethyl cellulose having 44.0-51% content of ethoxy groups and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

18. An extended release formulation according to claim 1 wherein the film coating composition is comprised of 85% by weight of ethyl cellulose having an ethoxy content of 44.0-51% and a viscosity of 50% cps for a 5% aqueous solution, and 15% by weight of hydroxypropylmethylcellulose having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12%.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose coated with a quantity of a mixture comprised of 85% ethyl cellulose and 15% hydroxypropylmethylcellulose sufficient to give coated spheroids having a dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C:

Time	Average % Venlafaxine HCl Released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides

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a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

21. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

23. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof,

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an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

24. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

25. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

* * * * *

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Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Serial No.: 09/884,412 Group Art No.: 1615
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AMENDMENT TRANSMITTAL LETTER

1. Enclosed please find the following documents for the above-identified application:
 - a. Response to Office Action mailed on January 14, 2002
 - b. Terminal Disclaimer

CERTIFICATE OF MAILING 37 CFR §1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number ET302331255US addressed to the Commissioner for Patents, Washington, DC 20231.

Date

4/15/02

Bubinea D. Owens

WYETH 002-000517

2. Fee calculation

CLAIMS AS AMENDED					
(1) FOR	(2) CLAIMS REMAINING AFTER AMENDMENT	(3) HIGHEST NUMBER PAID FOR	(4) NUMBER EXTRA x RATE		(5) ADDITIONAL FEE
TOTAL CLAIMS	6	20	0	x \$ 18.00	0.00
INDEPENDENT CLAIMS	6	3	3	x \$ 84.00	252.00
MULTIPLE DEPENDENCY FEE				\$ 280.00	
Total Amendment Fee:					\$252.00

Fee for filing terminal disclaimer under 37 C.F.R. 1.20(d) \$110.00

☒ Please charge Deposit Account No. 01-1425 for: \$362.00

The Commissioner is hereby authorized to charge any additional fees required by this paper, including the enclosed documents, and during the entire pendency of this application and to credit any excess amounts paid to Deposit Account No. 01-1425. A copy of this letter is enclosed for use by the Deposit Account Branch.

Respectfully submitted,

Rebecca R. Barrett

Rebecca R. Barrett
 Attorney for Applicants
 Reg. No. 35,152

Wyeth
 Patent Law Department
 Five Giralda Farms
 Madison, NJ 07940-0874
 Tel. No. (610) 902-2646



Docket No. AHP-95011DI-7/3/02

Patent

TECH CENTER 1600/2900

APR 19 2002

RECEIVED

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of: Deborah M. SHERMAN, et al.
Serial No.: 09/884,412 Group No.: 1615
Filed: June 19, 2001 Examiner: James M. Spear
For: EXTENDED RELEASE FORMULATION
Confirmation No.: 2298
Customer Number: 25291

Commissioner for Patents
Washington, DC 20231

AMENDMENT

This is in response to the Office Action issued in connection with this case on
January 14, 2002.

Please amend the application as follows:

In the Claims

Please cancel Claim 1, without prejudice.

Please add the following new claims:

3-25. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

04/18/2002 TBESHAH1 00000032 011425 09884412

01 FC:102 252.00 CH

WYETH 002-000519

83

B

Docket No: AHP-95011-D1

Patent

26. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

Claim 1 was rejected under 35 U.S.C. § 103. Claim 1 has been cancelled with prejudice, making this rejection moot.

27. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

28. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient. —

Rebecca R. Barrett

Remarks

Claims 1, 23 and 24 were pending in this case. Claims 1, 23 and 24 were rejected. Claims 25-28 were added to more fully claim Applicants' invention. No new matter was added by these claims.

Watson, NJ 07940-0874

Claims 23 and 24 were rejected under the doctrine of obviousness type double patenting as being unpatentable over Claims 20 and 21 of U.S. 6,274,171. The Examiner states that it would be reasonable to expect one skilled in the art to modify the dosage form and administer the venlafaxine spheroids as unencapsulated dosages. Applicants disagree with the Examiner's characterization of the invention

Docket No: AHP-95011 D1
Patent

and note that the claims are not limited simply to unencapsulated spheroids. However, to facilitate prosecution, Applicants have submitted herewith a terminal disclaimer, disclaiming any portion of this application beyond the term of the '171 patent.

Claim 1 was rejected under 35 U.S.C. §103. Claim 1 has been cancelled, without prejudice, making this rejection moot.

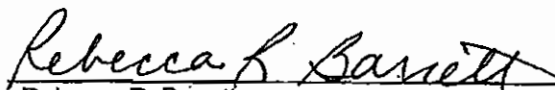
In view of the foregoing, Applicants respectfully maintain that Claims 23-28 are in condition ready for allowance and request an early and favorable Notice of Allowance.

CERTIFICATE OF MAILING 37 CFR §1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number ET 302331255US addressed to the Commissioner for Patents, Washington, DC 20231.

Date

Bubinea D. Owens


Rebecca R. Barrett

Reg. No. 35,152

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940-0874
Tel. No. (610) 902-2646



Docket No: AHP-95011 D1

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APR 19 2002
Patent
TECH CENTER (600/2900)

Version with Markings to Show Changes Made

Amend the application as follows:

Please cancel Claim 1, without prejudice.

Please add the following new claims:

—25. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

26. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

27. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

28. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of

WYETH 002-000522

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Docket No: AHP-95011 D1
Patent

venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient. --

04/15/2002 16:00 FAX 610 688 0273

WYETH PATENT DEPARTMENT

Docket No: AHP-95011 D1
PatentIN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of: Deborah M. SHERMAN, et al
Serial No.: 09/884,412 Group Art No.: 1615
Filed: June 19, 2001 Examiner: James M. Spear
For: EXTENDED RELEASE FORMULATION
Confirmation No.: 2298
Customer Number: 25291

Commissioner for Patents
Washington, DC 20231

FAX RECEIVED

APR 16 2002

GROUP 1600

OFFICIAL

Sir:

AMENDMENT TRANSMITTAL LETTER

1. Enclosed please find the following documents for the above-identified application:
 - a. Response to Office Action mailed on January 14, 2002
 - b. Terminal Disclaimer

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper and the documents referred to as enclosed therein are being facsimile transmitted with the United States Patent Office at 703-305-3592 on the date written below

April 15, 2002
Date

Rebecca Barrett
Rebecca Barrett

Docket No: AHP-95011 D1

Patent

2. Fee calculation


CLAIMS AS AMENDED					
(1) FOR	(2) CLAIMS REMAINING AFTER AMENDMENT	(3) HIGHEST NUMBER PAID FOR	(4) NUMBER EXTRA x RATE		(5) ADDITIONAL FEE
TOTAL CLAIMS	6	20	0	x \$ 18.00	0.00
INDEPENDENT CLAIMS	6	3	3	x \$ 84.00	252.00
MULTIPLE DEPENDENCY FEE				\$ 280.00	
Total Amendment Fee:					\$252.00

Fee for filing terminal disclaimer under 37 C.F.R. 1.20(d) \$110.00

☒ Please charge Deposit Account No. 01-1425 for: \$252.00

The Commissioner is hereby authorized to charge any additional fees required by this paper, including the enclosed documents, and during the entire pendency of this application and to credit any excess amounts paid to Deposit Account No. 01-1425. A copy of this letter is enclosed for use by the Deposit Account Branch.

Respectfully submitted,



Rebecca R. Barrett
Attorney for Applicants
Reg. No. 35,152

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940-0874
Tel. No. (610) 902-2646

04/15/2002 16:00 FAX 610 888 0273

WYETH PATENT DEPARTMENT

Docket No: AHP-95011 D1
PatentIN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of: Deborah M. SHERMAN, et al.
Serial No.: 09/884,412 Group No.: 1615
Filed: June 19, 2001 Examiner: James M. Spear
For: EXTENDED RELEASE FORMULATION
Confirmation No.: 2298
Customer Number: 25291

Commissioner for Patents
Washington, DC 20231

AMENDMENT

This is in response to the Office Action issued in connection with this case on
January 14, 2002.

Please amend the application as follows:

In the Claims

Please cancel Claim 1, without prejudice.

Please add the following new claims:

-25. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

AmendmentForm.dot - Rev 2/01

Page 1 of 5

Amendment

04/15/02 MON 17:01 [TX/RX NO 9479]

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WYETH 002-000526

4/15/2002 16:01 FAX 610 688 0273

WYETH PATENT DEPARTMENT

Docket No: AHP-95011 D1

Patent

26. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

27. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

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Remarks

Claims 1, 23 and 24 were pending in this case. Claims 1, 23 and 24 were rejected. Claims 25-28 were added to more fully claim Applicants' invention. No new matter was added by these claims.

Claims 23 and 24 were rejected under the doctrine of obviousness type double patenting as being unpatentable over Claims 20 and 21 of U.S. 6,274,171. The Examiner states that it would be reasonable to expect one skilled in the art to modify the dosage form and administer the venlafaxine spheroids as unencapsulated dosages. Applicants disagree with the Examiner's characterization of the invention.

AmendmentForm.doc - Rev 2/01

Page 2 of 5

Amendment

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04/15/02 MON 17:01 [TX/RX NO 9479]

WYETH 002-000527

04/15/2002 16:01 FAX 610 688 0273

WYETH PATENT DEPARTMENT

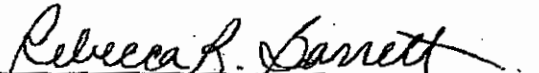
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Docket No: AHP-95011 D1
Patent

and note that the claims are not limited simply to unencapsulated spheroids. However, to facilitate prosecution, Applicants have submitted herewith a terminal disclaimer, disclaiming any portion of this application beyond the term of the '171 patent.

Claim 1 was rejected under 35 U.S.C. §103. Claim 1 has been cancelled, without prejudice, making this rejection moot.

In view of the foregoing, Applicants respectfully maintain that Claims 23-28 are in condition ready for allowance and request an early and favorable Notice of Allowance.


Rebecca R. Barrett

Reg. No. 35,152

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940-0874
Tel. No. (610) 902-2846

AmendmentForm.doc - Rev 2/01

Page 3 of 5

Amendment

04/15/02 MON 17:01 [TX/RX NO 9479]

B
WYETH 002-000528

Docket No: AHP-95011 D1
Patent

Version with Markings to Show Changes Made

Amend the application as follows:

Please cancel Claim 1, without prejudice.

Please add the following new claims:

-25. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

26. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

27. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

28. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of

Docket No: AHP-95011 D1
Patent

venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient. —



AHP-95011-D
PATENT
RECEIVED
APR 19 2002
TECH CENTER 1600/2900

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Sherman, et al.

Serial No.: 09/884,412

Examiner: Spear

Filed: June 19, 2001

Group: 1615

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, DC 20231

TERMINAL DISCLAIMER

Sir:

Your Petitioner, Wyeth, formerly American Home Products Corporation, a corporation duly organized and existing under the laws of the State of Delaware, with offices at Five Giralda Farms, Madison, New Jersey 07940-0874, the assignee of the entire right, title and interest in U.S. Patent 6,274,171 (by virtue of assignments recorded at Reel 011368, Frame 0195 and Reel 011866 Frame 0884) and U.S. Patent Application Serial No. 09/884,412 (by virtue of an assignment recorded at Reel 011368, Frame 0195 and Reel 011866 Frame 0884) does hereby disclaim the terminal part of any patent granted on U.S. Patent Application Serial No. 09/884,412 which would extend beyond the expiration date of the full statutory term, including any statutory extension thereof, as presently shortened by any terminal disclaimer, of U.S. Patent 6,274,171, except to the extent that the term of this Application Serial No. 09/884,412 might be extended pursuant to the Drug Price Competition and Patent Term Restoration Act of 1984 (35 USC 156) or any other applicable act of Congress.

Wyeth hereby agrees that any patent granted on U.S. Patent Application Serial No. 09/884,412 shall be enforceable only for and during such period that the legal title to U.S. Patent 6,274,171 shall be the same as the legal title to any patent granted on said U.S. Patent Application Serial No. 09/884,412, this agreement to run with any patent granted on said U.S. Patent Application Serial No. 09/884,412 and to be binding upon the grantee, its successors or assigns.

Wyeth does not disclaim any terminal part of any patent granted on this U.S. Patent Application Serial No. 09/884,412 prior to the expiration date of the full statutory term as presently shortened by any terminal disclaimer of U.S. Patent 6,274,171 in the event that later

04/16/2002 TRESHAM 00000032 011425 09884412
02 FC:146 110.00 CH

WYETH 002-000531

AHP-95011-D1
PATENT

said U.S. Patent 6,274,171 expires for failure to pay a maintenance fee, is held unenforceable, is found invalid, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR §1.321(a), has all claims canceled by a reexamination certificate, or is otherwise terminated prior to the expiration of its statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

Wyeth has reviewed the evidentiary documents submitted to establish its ownership of the patents and patent applications referred to in this Terminal Disclaimer and certifies that to the best of its knowledge and belief, title is in Wyeth, formerly American Home Products Corporation.

Petitioner hereby authorizes payment of the requisite fee for this Terminal Disclaimer pursuant to 37 C.F.R. §1.20 (d) by charging Deposit Account No. 01-1425. A duplicate copy of the transmittal letter is enclosed for deposit account charging purposes.

WYETH



Rebecca R. Barrett
Attorney of Record
for Wyeth
Reg. No. 35,152

Dated:
Telephone (610) 902-2646

WYETH 002-000532

AHP-95011-D/
PATENTIN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Sherman, et al:

Serial No.: 09/884,412

Examiner: Spear

Filed: June 19, 2001

Group: 1615

For: Extended Release Formulation

Assistant Commissioner for Patents
Washington, DC 20231TERMINAL DISCLAIMER

Sir:

Your Petitioner, Wyeth, formerly American Home Products Corporation, a corporation duly organized and existing under the laws of the State of Delaware, with offices at Five Giralda Farms, Madison, New Jersey 07940-0874, the assignee of the entire right, title and interest in U.S. Patent 6,274,171 (by virtue of assignments recorded at Reel 011368, Frame 0195 and Reel 011866 Frame 0884) and U.S. Patent Application Serial No. 09/884,412 (by virtue of an assignment recorded at Reel 011368, Frame 0195 and Reel 011866 Frame 0884) does hereby disclaim the terminal part of any patent granted on U.S. Patent Application Serial No. 09/884,412 which would extend beyond the expiration date of the full statutory term, including any statutory extension thereof, as presently shortened by any terminal disclaimer, of U.S. Patent 6,274,171, except to the extent that the term of this Application Serial No. 09/884,412 might be extended pursuant to the Drug Price Competition and Patent Term Restoration Act of 1984 (35 USC 156) or any other applicable act of Congress.

Wyeth hereby agrees that any patent granted on U.S. Patent Application Serial No. 09/884,412 shall be enforceable only for and during such period that the legal title to U.S. Patent 6,274,171 shall be the same as the legal title to any patent granted on said U.S. Patent Application Serial No. 09/884,412, this agreement to run with any patent granted on said U.S. Patent Application Serial No. 09/884,412 and to be binding upon the grantee, its successors or assigns.

Wyeth does not disclaim any terminal part of any patent granted on this U.S. Patent Application Serial No. 09/884,412 prior to the expiration date of the full statutory term as presently shortened by any terminal disclaimer of U.S. Patent 6,274,171 in the event that later

WYETH 002-000533


AHP-95011-D1
PATENT

said U.S. Patent 6,274,171 expires for failure to pay a maintenance fee, is held unenforceable, is found invalid, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR §1.321(a), has all claims canceled by a reexamination certificate, or is otherwise terminated prior to the expiration of its statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

Wyeth has reviewed the evidentiary documents submitted to establish its ownership of the patents and patent applications referred to in this Terminal Disclaimer and certifies that to the best of its knowledge and belief, title is in Wyeth, formerly American Home Products Corporation.

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WYETH



Rebecca R. Barrett
Attorney of Record
for Wyeth
Reg. No. 35,152

Dated: April 15, 2002
Telephone (610) 902-2646

Notice of AllowabilityApplication No.
09/884,412

Applicant(s)

SHERMAN, ET AL

Examiner

JAMES M. SPEAR

Art Unit

1615

—The MAILING DATE of this communication appears on the cover sheet with the correspondence address—

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to THE AMENDMENT AND DISCLAIMER FILED APRIL 15, 2002.2. ☒ The allowed claim(s) is/are 23-28.3. ☐ The drawings filed on _____ are acceptable as formal drawings.4. ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).a) ☐ All b) ☐ Some* c) ☐ None of the:1. ☐ Certified copies of the priority documents have been received.2. ☐ Certified copies of the priority documents have been received in Application No. _____.3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

5. ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

6. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.7. ☐ Applicant MUST submit NEW FORMAL DRAWINGS:(a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached1) ☐ hereto or 2) ☐ to Paper No. _____.(b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.(c) ☐ including changes required by the attached Examiner's Amendment/Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

8. ☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any reply to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)1 ☐ Notice of References Cited (PTO-892)3 ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)5 ☐ Information Disclosure Statement(s) (PTO-1449), Paper No(s). _____7 ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material9 ☐ Other2 ☐ Notice of Informal Patent Application (PTO-152)4 ☐ Interview Summary (PTO-413), Paper No. _____6 ☐ Examiner's Amendment/Comment8 ☐ Examiner's Statement of Reasons for Allowance

James M. Spear

JAMES M. SPEAR
PRIMARY EXAMINER
ART UNIT 1615



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

25291 7590 05/07/2002

WYETH
FIVE GIRALDA FARMS
MADISON, NJ 07940

EXAMINER

SPEAR, JAMES M

ART UNIT

CLASS-SUBCLASS

1615

424-489000

DATE MAILED: 05/07/2002

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,412	06/19/2001	Deborah M. Sherman		2298

TITLE OF INVENTION: EXTENDED RELEASE FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1280	\$300	\$1580	08/07/2002

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above. If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

B. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status.
See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

WYETH 002-000536

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** Box ISSUE FEE
 Commissioner for Patents
 Washington, D.C. 20231
Fax (703)746-4000

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 25291 7590 05/07/2002

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,412	06/19/2001	Deborah M. Sherman		2298

TITLE OF INVENTION: EXTENDED RELEASE FORMULATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1280	\$300	\$1580	08/07/2002

EXAMINER	ART UNIT	CLASS-SUBCLASS
SPEAR, JAMES M	1615	424-489000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

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2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
 2 _____
 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

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Commissioner for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

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(Date)

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PTOL-85 (REV. 04-02) Approved for use through 01/31/2004. OMB 0651-0033

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WYETH 002-000537



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,412	06/19/2001	Deborah M. Sherman		2298
25291	7590	05/07/2002		
WYETH FIVE GIRALDA FARMS MADISON, NJ 07940				
			EXAMINER SPEAR, JAMES M	
			ART UNIT 1615	PAPER NUMBER 7
DATE MAILED: 05/07/2002				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
 (application filed on or after May 29, 2000)

The patent term adjustment to date is 0 days. If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the term adjustment will be 0 days.

If a continued prosecution application (CPA) was filed in the above-identified application, the filing date that determines patent term adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) system. (<http://pair.uspto.gov>)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** **Box ISSUE FEE**
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Bubinea D. Owens

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Bubinea D. Owens
 Signature of Person Mailing Paper or Fee

APPLICATION NO.	FILED DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09844,412	06/19/2001	Deborah M. Sherman		2298

TITLE OF INVENTION: EXTENDED RELEASE FORMULATION

APPL. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1280	\$300	\$1580	08/07/2002

EXAMINER	ART UNIT	CLASS-SUBCLASS
SPEAR, JAMES M	1615	424-489000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.343).

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☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

Rebecca R. Barrett

2

3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE (CITY and STATE OR COUNTRY)

Wyeth

Madison, New Jersey

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(Authorized Signature)

Rebecca R. Barrett

(Date)

5/20/02

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01 FC:142

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02 FC:561

45.00 CH

03 FC:195

300.00 CH

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WEST**Freeform Search****Database:**

US Patents Full-Text Database
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JPO Abstracts Database
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Term:

venlafaxine and (peak)

Display: 10 Documents in **Display Format:** CIT **Starting with Number** 1**Generate:** ☐ Hit List ☒ Hit Count ☐ Image

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<u>DB Name</u>	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	venlafaxine and (peak)	44	<u>L2</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	venlafaxine and (peak adj blood)	2	<u>L1</u>

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Derwent World Patents Index
IBM Technical Disclosure Bulletins

Term:

12 and (ethylcellulose and
hydroxypropylmethylcellulose)

Display:**Documents in Display Format:****Starting with Number****Generate:**☐

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<u>DB Name</u>	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u>
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USPT,PGPB,JPAB,EPAB,DWPI,TDBD	12 and (coat or coating or coated)	106	<u>L7</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	12 and (coat or coating or coated)	106	<u>L6</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	14 and (coating or coated)	23	<u>L5</u>
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USPT,PGPB,JPAB,EPAB,DWPI,TDBD	venlafaxinecclm.	0	<u>L3</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	venlafaxine	187	<u>L2</u>
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	6274171.pn.	2	<u>L1</u>

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L1: Entry 1 of 2

File: USPT

Aug 14, 2001

US-PAT-NO: 6274171

DOCUMENT-IDENTIFIER: US 6274171 B1

TITLE: Extended release formulation of venlafaxine hydrochloride

DATE-ISSUED: August 14, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sherman; Deborah M.	Plattsburgh	NY		
Clark; John C.	Peru	NY		
Lamer; John U.	St. Albans	VT		
White; Steven A.	Champlain	NY		

US-CL-CURRENT: 424/461; 424/457, 424/458, 424/459, 514/781, 514/962

CLAIMS:

What is claimed is:

1. An extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing spheroids comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.
2. An extended release formulation of venlafaxine hydrochloride according to claim 1 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.
3. An extended release formulation according to claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.
4. An extended release formulation according to claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of

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WYETH 002-000542

hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. An extended release formulation according to claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1% to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

7. An extended release formulation according to claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. An extended release formulation according to claim 1 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

9. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

10. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37.degree. C:
Time (hours) Average % Venlafaxine HCl released
2 <30 4 30-55 8 55-80 12 65-90 24 >80

12. An extended release formulation according to claim 1 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose, and about 62% by weight of microcrystalline cellulose.

13. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

14. An extended release formulation according to claim 1 wherein the film coating comprises 6-8% by weight of total weight.

15. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

16. An extended release formulation according to claim 1

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WYETH 002-000543

wherein the film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

17. An extended release formulation according to claim 1 wherein the film coating composition is comprised of about 85% by total weight of film coating of ethyl cellulose having 44.0-51% content of ethoxy groups and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

18. An extended release formulation according to claim 1 wherein the film coating composition is comprised of 85% by weight of ethyl cellulose having an ethoxy content of 44.0-51% and a viscosity of 50% cps for a 5% aqueous solution, and 15% by weight of hydroxypropylmethylcellulose having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12%.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose coated with a quantity of a mixture comprised of 85% ethyl cellulose and 15% hydroxypropylmethylcellulose sufficient to give coated spheroids having a dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37.degree. C.:

Time Average % Venlafaxine HCl Released 2 <30 4 30-55 8 55-80 12 65-90 24 >80.

20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

21. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

23. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak

blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

24. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

25. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

CODE SHEET FOR CONTINUING DATA

LINE	CODE	SERIAL No.	FILING DATE	STATUS	DOCUMENT No.	ISSUE DATE
104	74	09/488,629	01-20-00	01	6,274,171	
105	82	08/964,328	11-05-97	03		
106	82	08/821,137	03-20-97	03		
107	68	60/014,006	03-25-96			
108						
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CONDITION AND STATUS CODES FOR CONTINUING DATA

CONDITION CODE

- 71 Continuation of application No.
81 which is a continuation of application No.
91 and a continuation of application No.
- 72 Continuation-in-part of application No.
82 which is a continuation-in-part of application No.
75 and a continuation-in-part of application No.
- 74 Division of application No.
84 which is a division of application No.
75 and a division of application No.
- 86, said application No.
89 Application No.
90 and application No.
92 each
- 65 filed as application No.
66 Substitute for application No.
68 Provisional application No.

STATUS CODE

- 01 Patent No.
03 abandoned
04 SIR No.

NOTE I: When the codes 86 and 92 are used, they must be followed by 81, 82 or 84 - conditions beginning with "which is"

NOTE II: Codes 71, 72 and 74 may be used only on the first line; one of them must be used on the first line in regular continuing data, 66 or 68 may be used on the first line in Substitute or Provisional cases. Remember, however, that if there is Provisional and other continuing data, the Provisional is always listed last.

CLAIMS ONLY

SERIAL NO.

FILING DATE

07684420-20 01

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT			*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.		IND.	DEP.	IND.	DEP.	IND.	DEP.
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47							97						
48							98						
49							99						
50							100						
TOTAL IND.	3						TOTAL IND.						
TOTAL DEP.							TOTAL DEP.						
TOTAL CLAIMS	3						TOTAL CLAIMS						

* MAY BE USED FOR ADDITIONAL CLAIMS OR ADMENDMENTS

WYETH 002-000547

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 2000

Application or Docket Number

09884612

CLAIMS AS FILED - PART I

(Column 1)

(Column 2)

SMALL ENTITY
TYPE ☐OR OTHER THAN
SMALL ENTITY

TOTAL CLAIMS	3	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	3 minus 20 =	0
INDEPENDENT CLAIMS	3 minus 3 =	0
MULTIPLE DEPENDENT CLAIM PRESENT <input type="checkbox"/>		

RATE	FEE
BASIC FEE	355.00
X\$9=	
X40=	
+135=	
TOTAL	

RATE	FEE
BASIC FEE	710.00
X\$18=	
X80=	
+270=	
TOTAL	710

If the difference in column 1 is less than zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

(Column 1)

(Column 2)

(Column 3)

AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
	Total	*	Minus	**
	Independent	*	Minus	***
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

SMALL ENTITY

OR OTHER THAN
SMALL ENTITY

RATE	ADDITIONAL FEE
X\$9=	
X40=	
+135=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
X\$18=	
X80=	
+270=	
TOTAL ADDIT. FEE	

AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
	Total	*	Minus	**
	Independent	*	Minus	***
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

RATE	ADDITIONAL FEE
X\$9=	
X40=	
+135=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
X\$18=	
X80=	
+270=	
TOTAL ADDIT. FEE	

AMENDMENT C	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA
	Total	*	Minus	**
	Independent	*	Minus	***
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM <input type="checkbox"/>			

RATE	ADDITIONAL FEE
X\$9=	
X40=	
+135=	
TOTAL ADDIT. FEE	

RATE	ADDITIONAL FEE
X\$18=	
X80=	
+270=	
TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."

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The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.



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Sherman et al.

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(54) **EXTENDED RELEASE FORMULATION OF
VENLAFAXINE HYDROCHLORIDE**

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424/461, 458, 459, 457, 456, 462, 489

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(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage
formulation and unit dosage form thereof of venlafaxine
hydrochloride, an antidepressant, which provides better con-
trol of blood plasma levels than conventional tablet formu-
lations which must be administered two or more times a day
and further provides a lower incidence of nausea and vom-
iting than the conventional tablets. More particularly, the
invention comprises an extended release formulation of
venlafaxine hydrochloride comprising a therapeutically
effective amount of venlafaxine hydrochloride in spheroids
comprised of venlafaxine hydrochloride, microcrystalline
cellulose and, optionally, hydroxypropylmethylcellulose
coated with a mixture of ethyl cellulose and hydroxypropyl-
methylcellulose.

6 Claims, No Drawings

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EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

This application is a divisional application of Ser. No. 09/488,629, filed Jan. 20, 2000 U.S. Pat. No. 6,274,171 which is a continuation-in-part of application Ser. No. 08/964,328, filed Nov. 5, 1997, now abandoned, which is a continuation-in-part of application Ser. No. 08/821,137, filed Mar. 20, 1997, now abandoned, which claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two

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or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydro-

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chloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride is polymorphic. Of the forms

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isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19-24% and a hydroxypropoxy content of 4-13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0-51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28-30% and a hydroxypropoxy content of 7-12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2-5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50-55° C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70% dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

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Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

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EXAMPLE NO. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1-4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%, w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug level. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to

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that of Table 1 are filled into pharmaceutically acceptable capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U.S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule			
Time (hours)	75 mg (IR) tablet (q 12h)	2 x 75 mg (ER) capsules (q 24hr)	1 x 150 mg (ER) capsules (q 24h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5

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TABLE 2-continued

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule			
Time (hours)	75 mg (IR) tablet (q 12h)	2 x 75 mg (ER) capsules (q 24hr)	1 x 150 mg (ER) capsules (q 24h)
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/mL, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/mL, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level			
Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsules
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from

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the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was to plastic tubes and stored at -20° C. until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 μ L of a stock internal standard solution (150 μ g/mL). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μ L portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μ L samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm \times 4.6 mm, 5 μ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately

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50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Ky. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/speronization machine (Aeromatic-Fieldier Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns:

Time/hr	% Dissolved 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcrystalline cellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that a peak blood plasma level of venlafaxine in from about 4 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

2. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine

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US 6,419,958 B2

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hydrochloride which comprises administering orally to a patient in need thereof, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 4 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

3. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

4. A method for providing a therapeutic drug plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

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5. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

6. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

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SEARCHED			
Class	Sub.	Date	Exmr.
424	495 494 461 458 459 457 456 462 489	1-13-02	8/2/02
Above To Date 5-6-02 8/2/02			

INTERFERENCE SEARCHED			
Class	Sub.	Date	Exmr.
424	495 494 461 458 459 457 456 462 489	5-6-02	8/2/02
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SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	Date	Exmr.
WEST 2.0	1-13-02	8/2/02

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CLASSIFICATION NOTES

Examiner/ Classifier	Class	Date	Initials

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ATTACH
DISK/FICHE/CD-ROM
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ISSUE SLIP STAPLE AREA (for additional cross references)

POSITION	INITIALS	ID NO.	DATE
FEE DETERMINATION	FL		6-22-01
O.I.P.E. CLASSIFIER		19	7-3-01
FORMALITY REVIEW	JAD	110	8-10-01
RESPONSE FORMALITY REVIEW			

INDEX OF CLAIMS

✓ Rejected N Non-elected
 = Allowed I Interference
 - (Through numeral)... Canceled A Appeal
 + Restricted O Objected

Claim	Final	Original	Date
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If more than 150 claims or 10 actions
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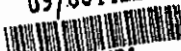
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09/884412

06/19/01

INITIALS

CONTENTS

Date Received
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or
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(Incl. C. of M.)
or
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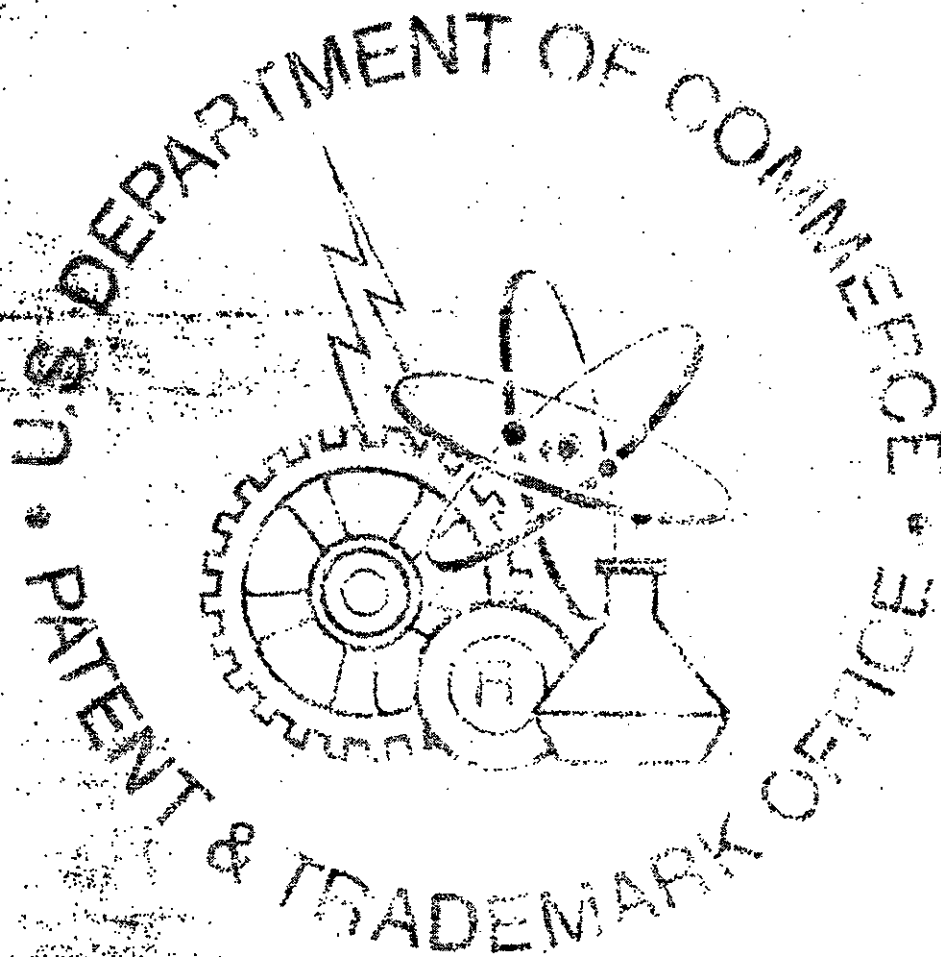
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WYETH 002-000560

1. COVERING COVER 1-800-265-6260
1/2" PTO 1899-5 for 2 1/2" 120" diameter



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